PATENT

921128-94537

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE THE APPLICATION OF)
)
Matthew Taylor et al.)
)
SERIAL NO.: 10/628,814)
)
FILED: July 28, 2003)
)
FOR: Airlift Pallet For Container Roll-In/Out Platform (CROP))
)

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450," on October 6, 2003.

Name of person signing Jamie L. Mueller

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In connection with the subject application, and in accordance with the provisions of 37 C.F.R. §§1.97 and 1.98, submitted herewith is a copy of form PTO-1449 containing a list of patents, publications, or other information submitted for consideration by the United States Patent and Trademark Office and copies of the references cited therein.

Respectfully submitted,

Date: 10-6-03

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INFORMATION DISCLOSURE CITATION

(Use several sheets if necessary)

Docket Number (Optional)	Application Number
920222-94537	10/628,814
Applicant(s) Matthew W. Taylor et al.	
Filing Date July 28, 2003	**Group Art Unit**

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL	REF	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
		3,545,713	12/08/70				
		4,049,135	09/20/77				
		4,537,540	08/27/85				
		4,758,123	07/19/88				
		5,810,186	09/22/98				
		6,622,640	09/23/03				

FOREIGN PATENT DOCUMENTS

	REF	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	Translation YES	Translation NO

OTHER DOCUMENTS *(Including Author, Title, Date, Pertinent Pages, Etc.)*

		A Multi-Modal Approach to Military Shipping, Defense Transportation Journal, February 2000, Pages 10-17
		M3 Flatrack, Container Roll-In/Out Platform (CROP) pamphlet

EXAMINER	DATE CONSIDERED

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP Section 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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OTHER DOCUMENTS *(Including Author, Title, Date, Pertinent Pages, Etc.)*

		Model 132 SR Screwdown Ractractable Twistlock drawing, Buffers USA, Inc.

EXAMINER	DATE CONSIDERED

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A Multi-Modal Approach to Military Shipping

While logistics is the subject of much attention during times of actual conflict, it is not an inherently glamorous subject, it is not close to the hearts of most warriors and it usually receives little attention during the interwar periods.[1]

However, this is no longer the exact situation. Since the close of the Persian Gulf War our logistics infrastructure and its component parts have been, and continue to be, improved upon.

Rapid response to a military contingency or crisis situation is the objective. This is now a well-established fact but its implementation is a major undertaking in several related areas. In the final phase it comes down to transportation capabilities and the movement of war-fighting materials from supply point of origin to forces in the field.

Our force structure has been significantly reduced. In keeping with this development—and the impact of a reduced defense budget—a smaller, more responsive logistics approach that requires less investment and money to operate is being aggressively pursued.[2]

Efforts to create smaller, more responsive logistics are underway in the Army under the name of Velocity Management and in the Air Force Lean Logistics. The goal of Velocity Management is to make the Army Logistics as fast and efficient as in a Fortune 500 company. Velocity Management, which focuses on responsiveness, postulates that moving supplies is cheaper than stockpiling.[3]

The Air Force's Lean Logistics objective is to move from an inventory-based system to a transportation-based system. The objective of both Velocity Management and Lean Logistics is to improve responsiveness while reducing costs, facilities, and personnel.[4]

The Military Traffic Management Command (MTMC) is also active in this area. In November 1999 MTMC formerly solicited bids for a domestic freight distribution contract valued at $30 million. The contract will cover Georgia, Alabama, and Florida. The logistics provider who wins the contract will start by distributing products most commonly associated with military operations; ship parts, aircraft parts, medical equipment, and vehicle parts. The award announcement is expected in the first quarter of 2000.[9]

The preceding discussion is intended to establish the point—if not the fact—that the Department of Defense is well on the way to reengineering its logistic structure and practices. On the surface these objectives may seem to resemble the accomplishments of the Fortune 500 companies. The reality is that the military is characterized by a detailed chain of command involving a myriad of responsibilities that tie together all the branches of the Armed Forces.[10]

The purpose of this paper is to propose a new transportation system that will augment and support many of the new Department of Defense programs either in existence, in development, or in the planning stage. This proposal is a combination of an operating system and new hardware.

The operating system is sea-air/air-sea combined routing. The hardware is the Container Air Mobile Platform (CAMP)

No matter what the area or intended purpose, any discussion involving the basic elements of unitization, pallets, containers, handling equipment, and chassis, will include specifications and dimensions. There is no way to escape this, and at the same time produce a meaningful paper.

THE CONTAINER AIR MOBILE PLATFORM

figure 1

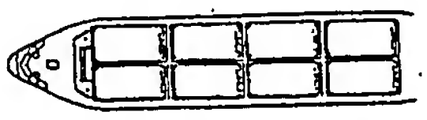
DIMENSIONS	FEET/INCHES	INCHES	MILLIMETERS
Exterior length	19'-3"	231"	5,867
Exterior height	10"	10"	254
Exterior width	7'-7½"	91 ½"	2,324
Useable Deck Length	18'-2"	218"	5,537
Interior usable Cargo Height w/min. 2" header clearance	6'-5"	77"	1,956
Useable Deck Width	7'-5"	89"	2,261

WEIGHT	POUNDS	TONS	KILOGRAMS
Tare	2,000	1.0	9,072
Payload	30,250	15.13	13,721.4
Gross Weight	32,250	16.13	14,682.6
Full Height Cubic Capacity	866 cubic ft	24.51 cubic feet	

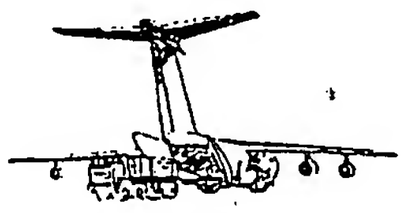
• The CAMP is specifically designed for military operations. It can be loaded, transported, and off-loaded on the palletized load system (PLS) truck, on a Container Roll Out Platform (CROP), a K-loader, the 23-ft. ISO chassis trailer, and the Air Force C-17 Globemaster III.

• To expand on the C-17 compatibility. The 88-inch wide rail system on the cargo deck permits eight Container Air Mobile Platforms to be loaded and transported in one lift.

figure 2



Platforms in a C-17 Cargo Bay



CAMP is loaded in a self-unloading Straight Truck, or K-Loader, that pushes the container directly into the aircraft

• In the commercial sector the CAMP can be transported in a 20-ft. ISO container (or two in a 40-footer) for a containership lift; in a straight or semi-truck trailer; or 14 CAMPS on the main deck of a Boeing 747-400

• Once it is understood—and the concept of air-sea/sea-air combined routing accepted—the Container Air Mobile Platform will be instrumental in creating this new third mode.

This air-surface intermodal capability will, for the first time, permit military shipments to travel from origin to destination in a combined routing, thus avoiding reloading the shipment—from one mode to another—while in transit. Loaded in the CAMP, a shipment would move over continents and littoral areas by air, on the open sea by fast containership, with truck and rail as the connecting links. This would shift some of the burden of priority cargo lift away from the assets of the Air Mobility Command and the Civil Reserve Air Fleet.

The question naturally arises as to what kind of military supplies and equipment would move in this new air-sea/sea-air combined routing system. The best possible answer at this time is: those supplies and equipment that do not have sufficient priority for origin-to-destination air lift for—but would contribute substantially to—the success of the mission, with their earlier arrival by several days over conventional land and sea routing.

Following is what might be called a high-probability list of air-sea/sea-air combined routing cargo for an overseas military operation:

Army tactical missile system pods
Multiple launch rocket system pods
Electronic and communications equipment
Skid-mounted machinery
(such as generators and laundry equipment)
Small-size vehicles
Field hospitals
Field rations
Hand-held weapons

Admittedly, this list does not conform to the Commodity Class structure found in current logistics tables—nor does it conform to doctrine—but for a starting point it will serve the purpose.

All of the above cargo types are of such size and weight as to be transported on a Container Air Mobile Platform. The above list is basically for illustration purposes. Other equipment and supplies with similar size and weight characteristics could also be transported in this new system. The most important consideration is what is needed in the field and how soon it can be delivered, within size and weight limitations of the CAMP unit.

Although the Container Air Mobile Platform has many advantages, it also has limitations. Army and Marine Corps tanks, heavy trucks, and construction equipment are not intended for the CAMP system. Their weight and handling requirements are beyond the capacity of this new concept. Heavy equipment will continue to load into ships of the pre-positioning squadrons and the fast sealift ships of the Military Sealift Command.

While Container Air Mobile Platforms will shorten transit times in the logistics pipeline, they will create their own set of requirements; such as tracking, accounting and program management.

Upon completion of a combined rout-

ing movement, and shipment deli[illegible], there will be the problem of empty equipment return. The CAMP, unlike an ISO container, is not a space consumer or a handling problem. Eight empty CAMP units can be stacked and locked together and handled as one unit.

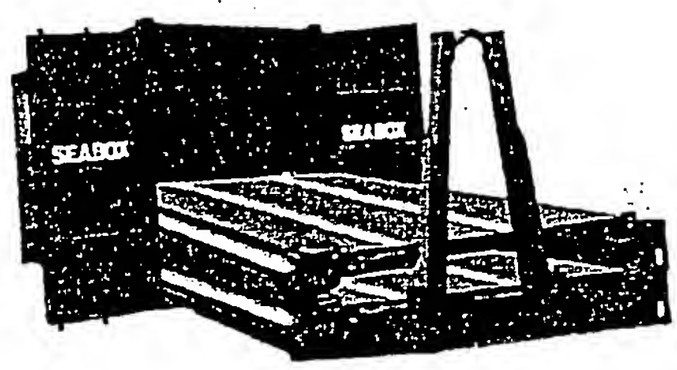
CAMP units should be removed from the combat area as soon as possible after off-loading. They should be returned to CONUS or an overseas supply depot where they would be available for another load-out. An alternative use would be for a retrograde cargo lift should there be a requirement for such a service.

The empty CAMP lends itself to return movement from overseas and positioning within CONUS, in what is possibly the most efficient and economical operation of all intermodal equipment repositioning, when we consider that:

- 8 empty CAMP units will load into one 20-ft. ISO container
- 16 empty CAMP units will load into one 40-ft. ISO container
- 16 empty CAMP units will load onto one 40-ft. flatbed semi-trailer
- 64 empty CAMP units will load into an Air Force C-17 Globemaster III
- 90 to 112 empty CAMP units will load on the main deck of a Boeing 747-400

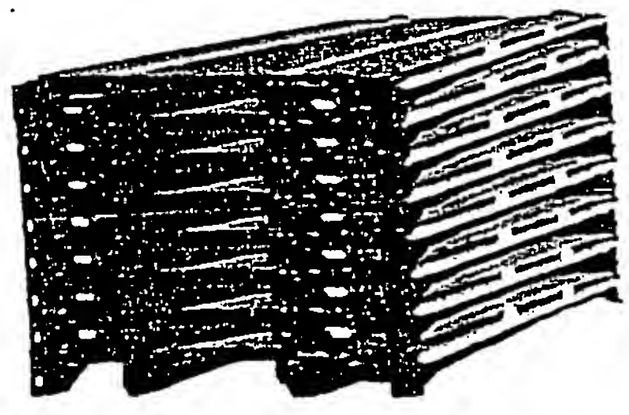
In a maximum effort high volume operation—such as the Persian Gulf War—when there would be an immediate need in CONUS for Container Air Mobile Platforms for follow-on shipments, the empty units could be returned in a reverse air-sea combined routing. In a less intensive scenario, depending upon short- or long-term needs, a given number of CAMP units could return in an all sea routing. This is but one of the many flexibilities in the CAMP program.

The CAMP Program is not intended, nor is the concept capable of, replacing existing container and intermodal cargo handling systems. The ISO container and its infrastructure—both military and commercial—will con-



above: CAMP inserted into a 20' ISO Shipping Container on top of the PLS CROP.

right: CAMP stacked 8-high



"If funded and implemented, the Container Air Mobile Platform and combined routing will be a 'first' for the Department of Defense. There is nothing in the private sector that even approaches this concept and its potential."

tinue to be the mainstay in supporting overseas operations and deployments. The Container Air Mobile Platform is designed to provide a service not otherwise available: to get priority supplies and equipment where needed, faster, to fill the gap between air and sea transport until the operation is secure or its objectives have been met.

If funded and implemented, the Container Air Mobile Platform and combined routing will be a 'first' for the Department of Defense. There is nothing in the private sector that even approaches this concept and its potential.

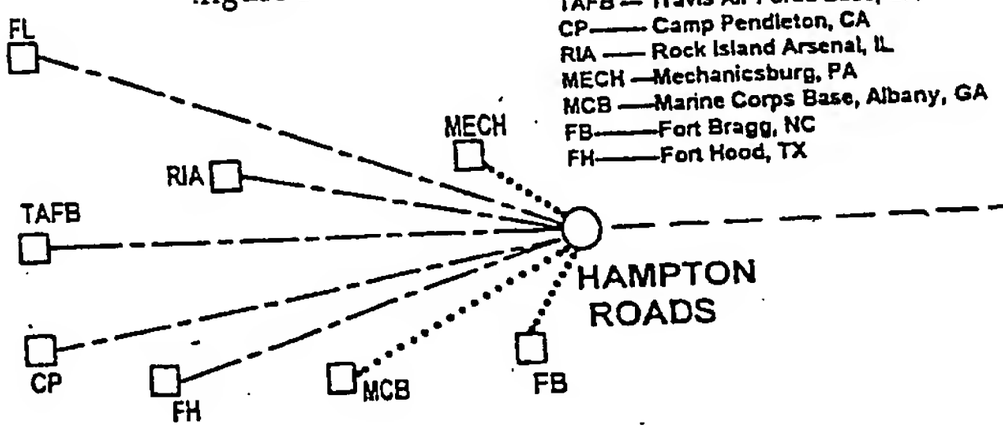
airlift, and then by ...st container ships on the open sea. The objective is easily within our reach and in the process of development will produce efficiencies and economies not even visualized at this time. Even now, in the private sector, commercial container shipments move from Chicago to London, by way of Montreal, in eight days.

OPERATIONS

Operations is the word that covers a multitude of activities in the broad field of transportation. In one respect the operating cycle of the CAMP will resemble that of a container belonging to a commercial container leasing company. A container is leased by and delivered to an ocean carrier at point A, who will load the container for shipment to point B. Upon arrival at point B the shipment is devanned and the empty container returned to the leasing company at point C.

Unlike the leasing company who takes delivery of its container and then leases it to another user, the CAMP remains in the custody of the receiving command until it

.figure 3

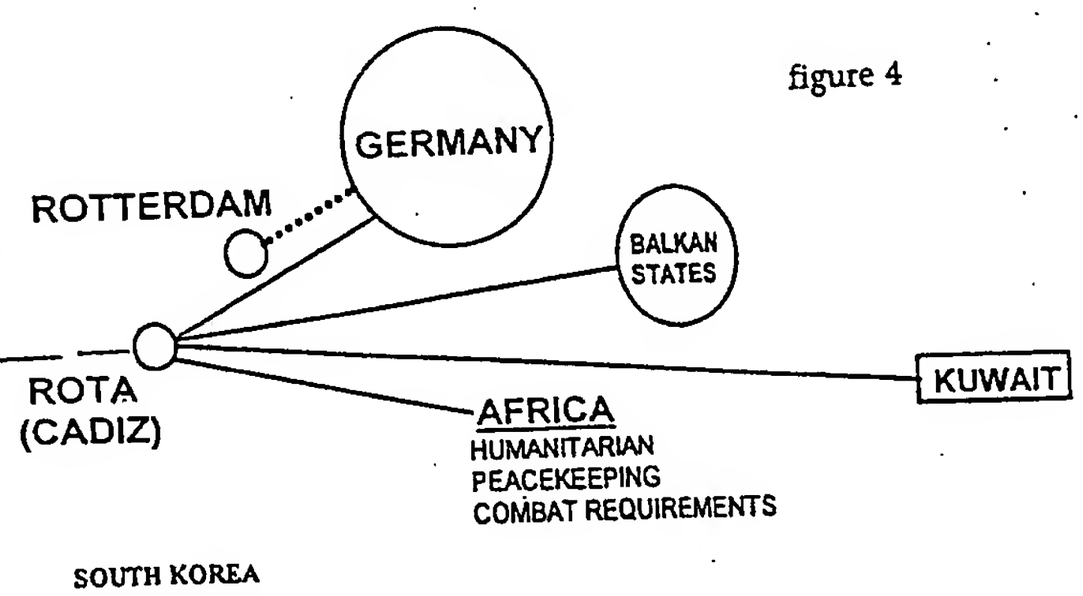


POINTS OF MILITARY CARGO ORIGIN
FL—— Fort Lewis, WA
TAFB — Travis Air Force Base, CA
CP—— Camp Pendleton, CA
RIA —— Rock Island Arsenal, IL
MECH —Mechanicsburg, PA
MCB —Marine Corps Base, Albany, GA
FB——Fort Bragg, NC
FH——Fort Hood, TX

FIGURE 1

First Air Lift	1 day
Hampton Roads Dwell Time	1-2 days
Ocean transit	6 days
Rota Dwell Time	1-2 days
Second Air Lift	1 day
Total Transit	10-12 days

figure 4



As it is intermodal equipment, the Container Air Mobile Platform inventory should be assigned to the Military Traffic Management Command, headquartered in Falls Church, Virginia. Operational control could be assigned to the Deployment Support Command at Fort Eustis, Virginia. Because of its location this command would be a logical choice for managing the day-to-day operations of a CAMP Program.

The CAMP will provide the means and air-sea combined routing will provide the method. Basically, the method is a combination of transport modes, linked together in sequence, from shipment point of origin to consignee destination. It is new equipment—the CAMP—imposed on existing transport capabilities.

- Main Deck Cargo Aircraft (the C-17 and Boeing 747-400)
- Trucks—closed vans for loaded CAMPS and flatbeds for positioning empty CAMPS
- Container ships and Roll-on/Roll-off ships

COMBINED ROUTING

The objective of combined routing will be to compress transit times over a large land mass and littoral areas with

is ordered out of the area for return to the U.S., or to an overseas supply depot for further use. This places the CAMP in a closed-loop operation that will travel only within a predetermined number of geographical locations.

THE MILITARY SUPPLY CHAIN

The sea-air combined routing system would be used to support combat operations, peacekeeping forces, and humanitarian needs. Routings would be structured to link supply points in the U.S. to destinations overseas, as events may require.

The military and economic advantages of this new system point to future success with easily identified savings. At five cents a ton-mile ocean shipping is not expensive but transit times leave much to be desired. Air freight is about $.50 a ton mile with transit times averaging three to four days. The difference in cost between the two—and the transit time advantage—will be the economic driving force favoring this new system.

THE ROUTE STRUCTURE

Figure (3) is an outline map designed to illustrate the air-sea combined routing arrangement. CAMPs would be

positioned to any military base wi. .1 pending shipment for any of the European or Middle East destinations shown on the right. From the western part of the U.S. the loaded CAMPs would be airlifted to a military air base or commercial air port in the Hampton Roads area. Once off-loaded, the CAMPs would be trucked to the Naval Base or marine terminal for loading aboard ship for the ocean transit. The destination would be the U.S. Naval Base at Rota, Spain. The Spanish port of Cadiz could serve as an alternate port should the facilities at Rota be taxed to capacity or otherwise not available.

DWELL TIME

Dwell time is defined as transfer time between modes. Unlike airlift and ocean transit times which are relatively fixed in duration, dwell time will depend on coordinated scheduling that must be planned in advance. Basically, it is a matter of airlift arrival and ship departure in the Hampton Roads area, followed some six or seven days later by ship arrival at and airlift departure from Rota.

The transfer of loaded CAMPs from an Air Base or commercial airport should be no different from any other local delivery in the Hampton Roads area; although there may be a need for a priority delivery arrangement at an ocean carrier's marine terminal receiving gate.

SOUTH KOREA

Should North Korea launch an attack on South Korea, immediate reinforcements on the Korean Peninsula would have the highest priority. U.S. and South Korean forces would need to be sustained to the point where they could halt the North Korean attack and launch a counter offensive. Much of the military equipment is already in place, as well as on board ships of the Military Sealift Command pre-positioning squadrons. Air-sea combined routing can fill the gap between rather lengthy Pacific Ocean transit times and the excessive demands that, concurrently, would be placed on airlift assets.

The air-sea combined routing for Korea, by way of Japan, would be a reverse direction of the outlined map (Figure 3). From the various home stations or military cargo points of origin, the domestic air lift routes would converge on Seattle and Tacoma, Washington. CAMPs would then be transferred to commercial containerships for transit to major Japanese ports and then by airlift to destination in South Korea. This will permit selective destination routing by air in coordination with any recent tactical changes, or as the current combat situation may require.

AIRLIFT AND OCEAN TRANSPORT

Within the continental United States, the air shipping of cargo-laden CAMPs could move in either Air Force or commercial aircraft. With the capability to load eight CAMPs in one lift, the C-17 Globemaster III becomes the carrier of choice.

Loading CAMPs in the aircraft, transport and delivery from home station to the sealift port of embarkation should be a rather straightforward operation, requiring no more attention than any other shipment of the same physical characteristics.

Ocean transport is a somewhat different matter. The difference is brought about by the type of services available rather than mode characteristics. Navy ships would be the most probable carriers of CAMPs from Norfolk to Rota. In the Pacific, CAMP units would move on commercial containerships ..lany of which are foreign flag—from Seattle/Tacoma to major Japanese ports. Pacific transit times will average ten days. Air-sea combined routing from home station to the Korean Peninsula will take 16 days providing there is no excessive dwell time involved.

In the Atlantic, ships of the Naval Fleet Auxiliary Force of the Military Sealift Command frequently transit to and from the Mediterranean Sea. An eastbound voyage deviation to call at Rota would not consume excessive time.[2] Other Navy ships, or ships under Navy control, may also be available for this most important sealift. This would be an irregular service at best but for normal peacetime non-contingency operations it should suffice; at least for the start-up phase. [12]

ATLANTIC CONTAINERSHIP SERVICES

Commercial containership services from Hampton Roads direct to Cadiz do not exist at this time. But there is the possibility that should an air-sea combined routing system be implemented, with sufficient air-sea cargo volume, a U.S. flag ocean carrier might be induced to offer a weekly eastbound service to both Rota and Cadiz. The assumption is made that the carrier would also solicit commercial cargo for Cadiz and any additional Department of Defense cargo for Rota, in addition to the core cargo of CAMPs.

Such a development would be highly advantageous. In the event of any full-scale military operations in the Persian Gulf or eastern Mediterranean, the ocean carriers' service could be expanded rapidly to meet the greatly increased requirements that would most certainly come about. [13]

DISTRIBUTION/MANAGEMENT

The employment of CAMP equipment throughout the Armed Forces would be a matter of priority. Maximum utilization would occur in the event of a military operation in the Persian Gulf or on the Korean Peninsula. Secondary assignments, based on reserve pool availability, would be allocated to savings and efficiency (routine lifts); critical needs (humanitarian and peacekeeping); and expanded usage (training exercises), see Figure 5.

CONTAINER AIR MOBILE PLATFORM INVENTORY

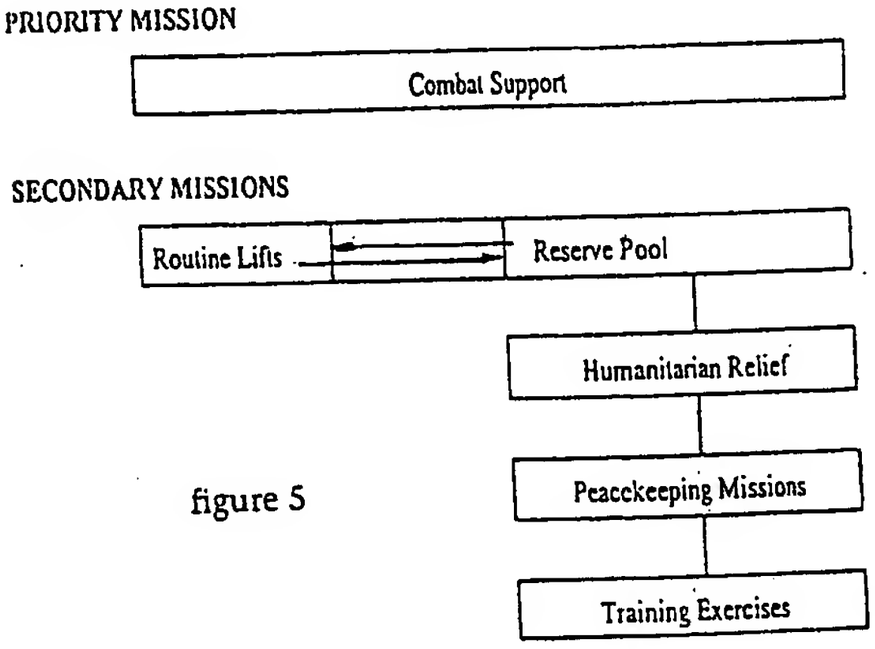


figure 5

As mentioned in Part I, the Deployment Support Command at Fort Eustis, Virginia, would be the logical

choice for the administration, op. .ional, and technical management of the Container Air Mobile Platform inventory and program. The proximity to naval facilities, containership terminals, airports (both commercial and military), and the supporting infrastructures comprises an ideal combination.

By routing all CAMP movements through the Hampton Roads area, trucking between modes should be 100% effective. As the only interchange point between CONUS origin and overseas destinations, maximum movement control would be achieved.

A Container Air Mobile Platform operating command would have charge of the following:

1. Supply CAMP units to Army, Air Force, Navy and Marine Corps units who have overseas shipping requirements where CAMP units can reduce delivery time.

2. Arrange ocean transport with the Military Sealift Command, or with commercial carriers for Rota (Spain) delivery.

3. Coordinate arrival of CAMP units from inland points of origin into the Hampton Roads area and delivery to either the Norfolk Naval Base (MSC loading) or commercial marine terminals.

4. Take custody of all CAMP equipment not in use; store and maintain.

The purpose of this intentionally tight, hands on management, is to ensure movement control of the CAMPs and identification of the shipment it is carrying. This is to prevent what happened in the Persian Gulf War when containers arrived in-theater with no identifying information as to the contents or to whom the container should be delivered. [5]

This has been overcome by the implementation of a series of in-transit visibility (ITV) systems which comprise the U.S. Transportation Command's Global Transportation Network, the Defense Automatic Addressing System–CONUS Freight Management, the Air Force Consolidated Aerial Port System II, and the Army Movements Management System. [6]

To facilitate implementation, two radio frequency tags are affixed when a loaded CAMP departs its point of origin or home station. The first tag will be attached to the Container Air Mobile Platform, and the second tag to the shipment on the unit.

Once landed at the U.S. Naval Base in Rota, the CAMP would be air lifted to a destination in the general vicinity of the combat zone or peacekeeping operation. At this point intratheater land transportation becomes a factor as the cargo-laden CAMP must be delivered to the designated command. [7]

Once delivered, the frequency tag identifying the shipment is removed. The tag attached to the CAMP (unit) now becomes the sole source for tracking future movements as the unit enters its redeployment phase.

SUMMARY

The Container Air Mobile Platform and combined routing have been discussed in as much detail as possible. Anyone experienced in intermodal hardware and concept development will recognize that while some technical problems remain, they will be minor in nature and should be easily solved. It is a concept that integrates with existing intermodal equipment and systems as well as being flexible in meeting customer needs.

The Container Air Mobile Platform is not offered as a 'single solution' to gistics transport problems but rather as a concept that will take its place alongside existing equipment in the Department of Defense inventory, performing a service never before available for the movement of critical materials in a compressed time frame.

If thoroughly and properly implemented, the Container Air Mobile Platform will become an important part of our logistics transportation infrastructure. The best statement, or definition of this objective—as seen by the writers—is to be found in General John M. Shalikashvili, U.S. Army (Ret), Joint Vision 2010 statement. [8]

"Focused logistics will be the fusion of information, logistics and transportation technologies to provide rapid crisis response, to track and shift assets even while en route, and to deliver tailored logistics packages and sustained directly at the strategic, operational, and tactical level of operations. Information technologies will enhance airlift, sealift, and prepositioning capabilities to lighten deployment loads and assist pinpointing logistics delivery systems currently in the inventory. The combined impact of these improvements will be a smaller, more capable deployed force. It will require less continuous support with a smaller logistics footprint, decreasing the vulnerability of U.S. logistics lines of communication."

To the extent the Container Air Mobile Platform will contribute to any of the above named missions, it will more than serve its purpose. ***DTJ***

George D. Saunders has an extensive background in the steamship agency and container leasing business in both New York and California, followed by a stint with the Military Sealift Command in Washington, D.C. In recent years he has devoted considerable attention to the intermodal shipping aspects of military logistics. He is a graduate of the Naval War College and has served in the United States Navy.

Jim Brennan, Jr., is President and CEO of Sea Box, Inc.; a leader in custom design and integration of ISO container shelters, and is a major supplier of new and used ISO containers and chassis to the military, as well as private industry since 1983. Mr. Brennan holds two patents on the CROP platform, which folds and nests, that is used by the US Army on PLS Trucks.

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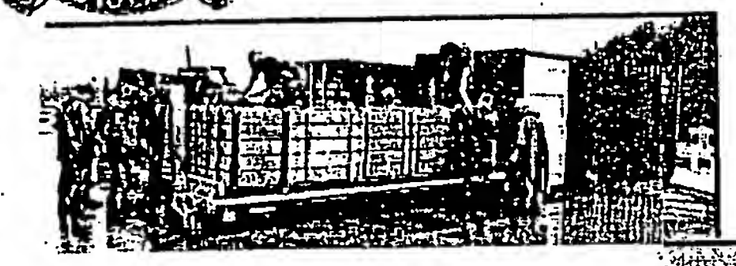
TEAM HTV

M3 Flatrack, Container Roll-in/Out Platform (CROP)



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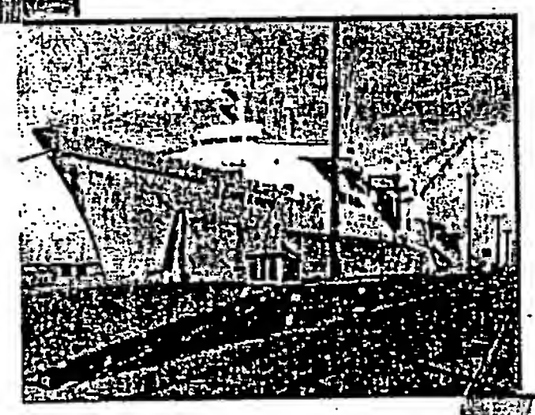
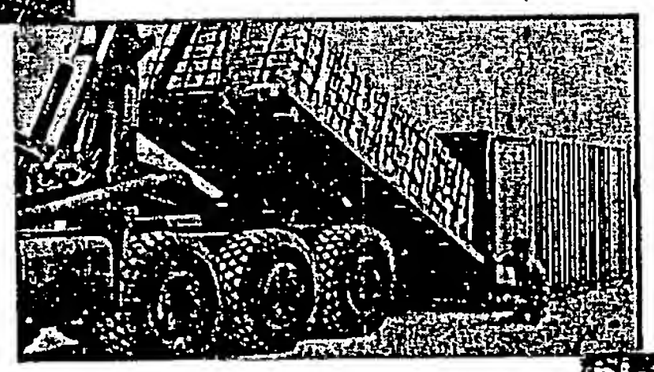


Shipping Container



Removing CROP from Container

Description

The CROP is a NATO compatible flatrack that allows intermodal transport of all classes of supply while secured in a 20 foot ISO container. The CROP payload is higher than the M1 when loaded on the PLS or HEMTT LHS. The CROP allows a true factory to foxhole distribution or supply with minimal or no MHE handling. Shipments can be configured in CONUS and moved to front line units without reconfiguration or removal from the platform. Shipment back to CONUS is accomplished by folding down the A-frame, stacking 5 CROPs on the bottom CROP (with A-frame up) and inserting into a container. Intermodal shipments are more secure and less costly than breakbulk shipments. Shipment by container keeps the platform and supplies out of the weather. The CROP is galvanized for longer life and lower lifecycle cost.

Characteristics

- NATO Interoperable (STANAG 2413)
- Gross Weight Rating: 36,250 lbs
- Payload: 32,250 lbs
- Fits inside a 20 foot ISO container
- No Dunnage Required for CROP in Container
- PLS or HEMTT LHS extracts CROP from Container
- Folding A-frame for Retrograde 6 High Stack in 8.5' ISO Container

Dimension Comparison

	M3	M3A1
Width	91.25	91.50
Height A-frame down	17.04	17.22
Height A-frame Up	71.50	71.50
Length	233.27	233.36
Weight	3800 lbs	4000 lbs

Off Loaded to Troops

Retrograde

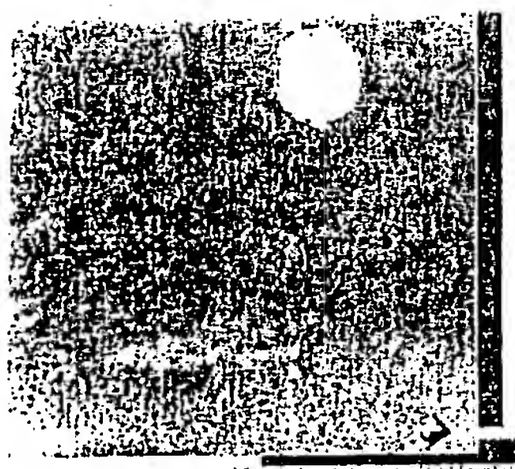
General Information

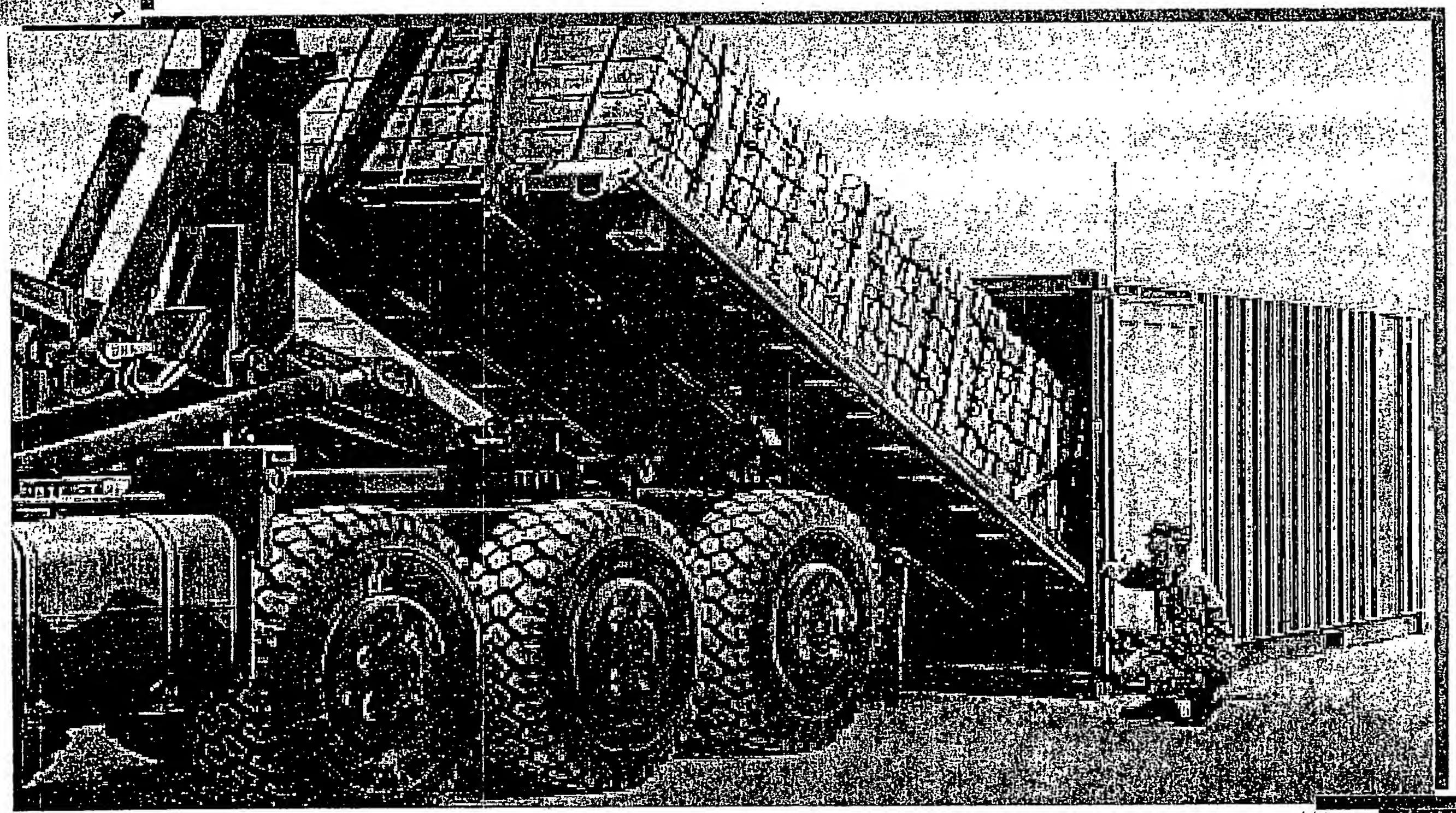
- Manufactured by:
  - Summa Technology (M3)
  - Hyundai Precision America (M3A1)
- 100% Option
- Requirement: 59,962 Total Flatrack
- FUE: 1Q FY00

Primary Mission

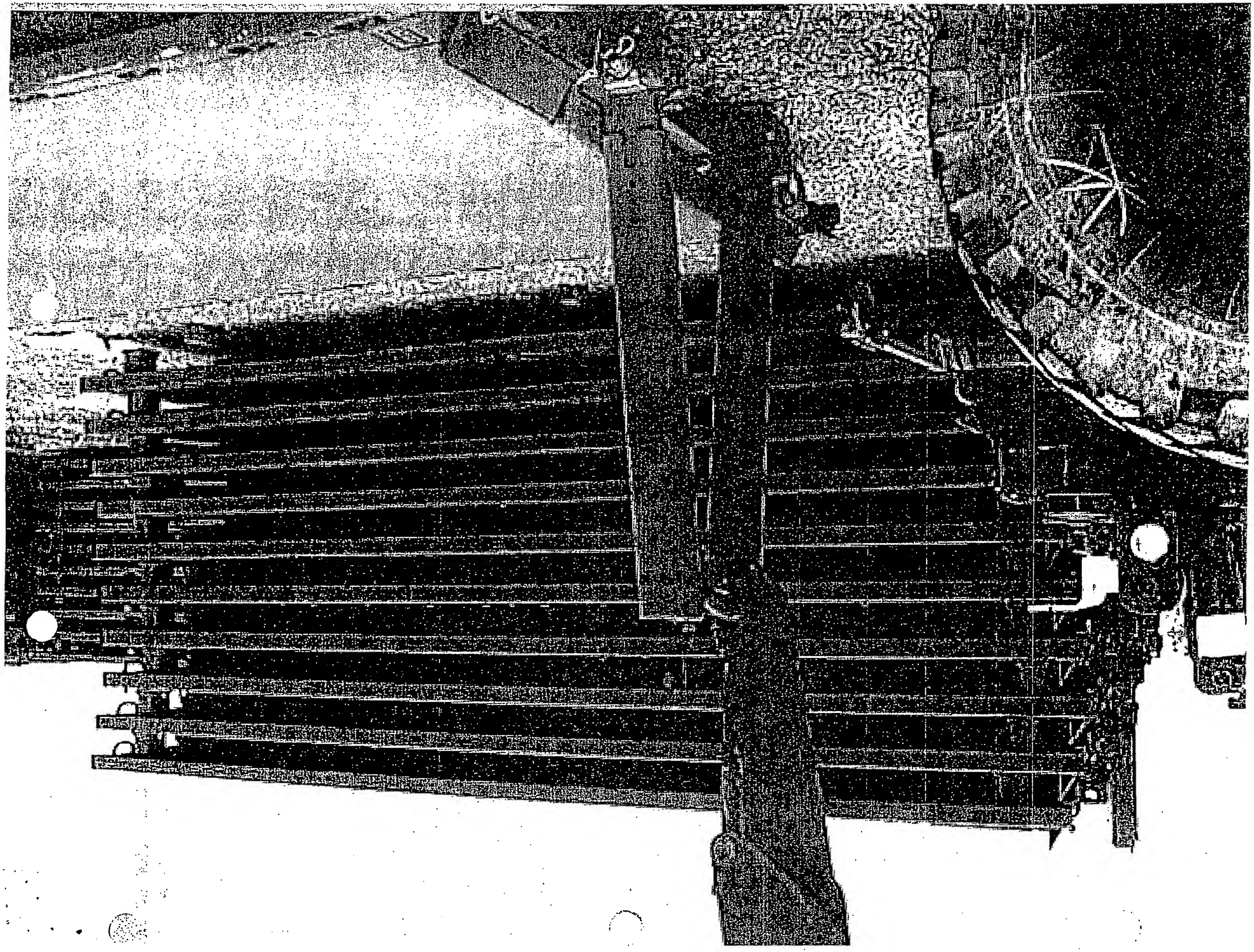
- Provide a Means to Ship Strategic Configured Loads from Depot to the End User

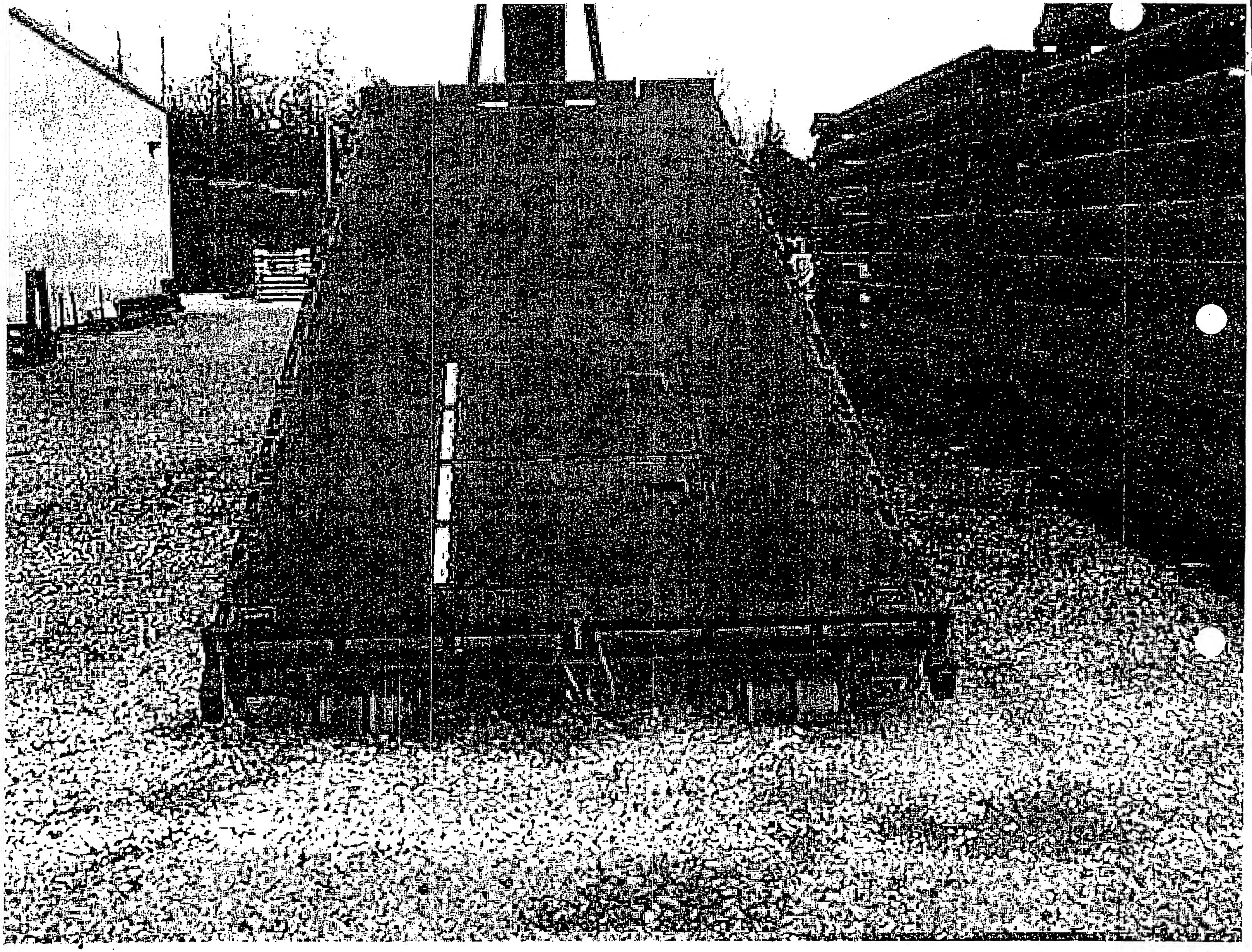
"Force XXI Must Have Enabler"

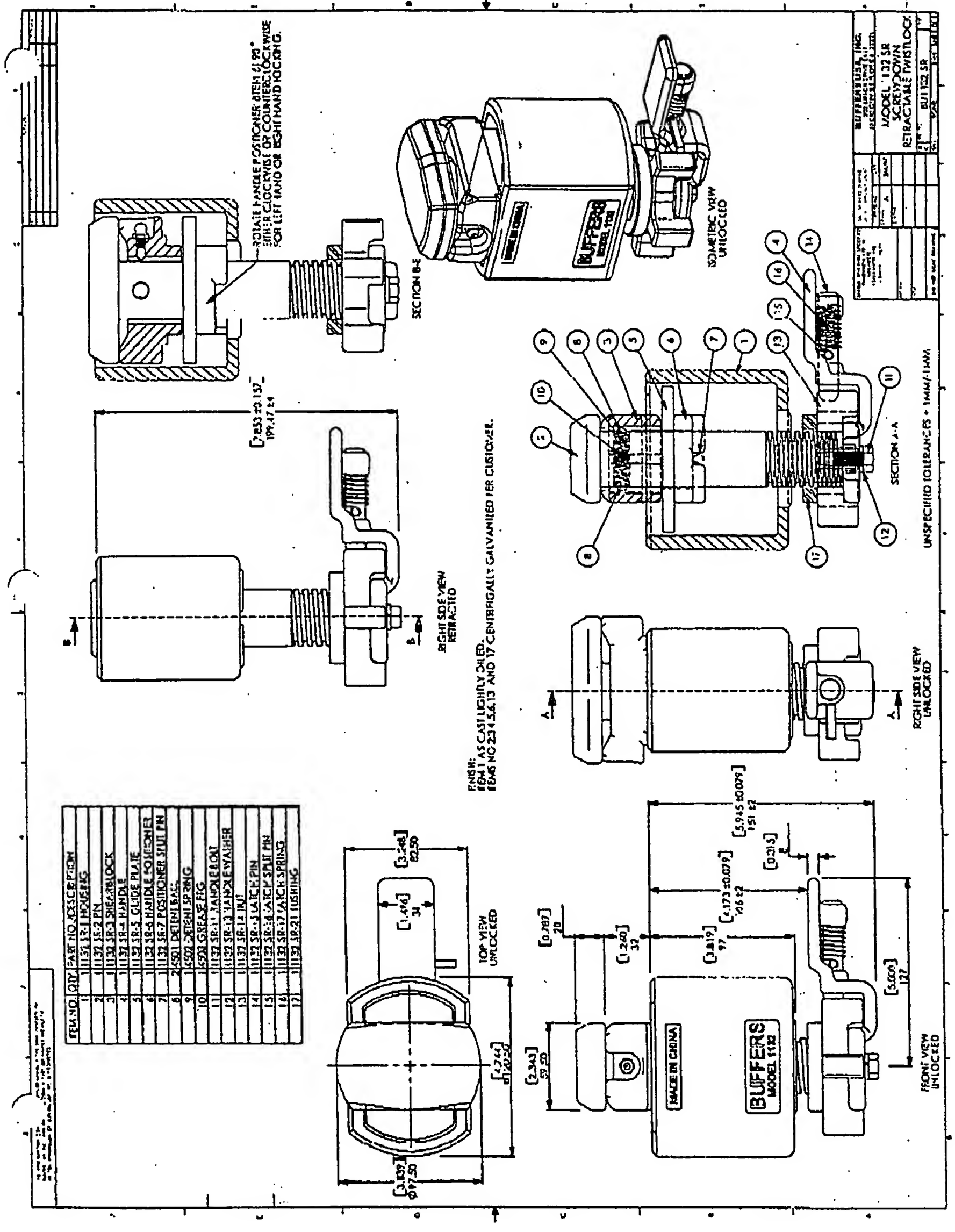




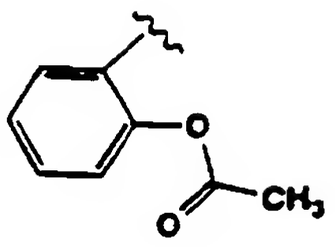
Removing CROP from Container

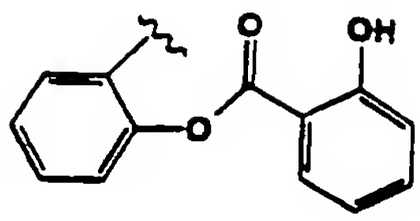


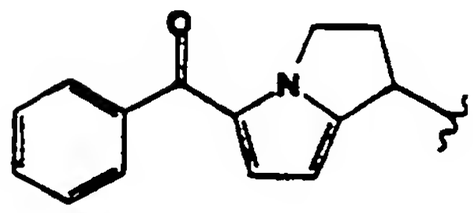




ITEM NO.	QTY	PART NO./DESCRIPTION
1	1	1132 SR-1 HOUSING
2	1	1132 SR-2 PIN
3	1	1132 SR-3 SPEAR BLOCK
4	1	1132 SR-4 HANDLE
5	1	1132 SR-5 GUIDE PLATE
6	1	1132 SR-6 HANDLE POSITIONER
7	1	1132 SR-7 POSITIONER STUD PIN
9	2	1501 DETENT BALL
10	1	1502 DETENT SPRING
11	1	1503 GREASE FIG
12	1	1132 SR-11 HANDLE BOLT
13	1	1132 SR-12 HANDLE WASHER
14	1	1132 SR-13 INJ
15	1	1132 SR-14 LATCH PIN
16	1	1132 SR-15 LATCH STUD PIN
17	1	1132 SR-16 LATCH SPRING
12	1	1132 SR-21 BUSHING

(5) 

(6) 

(7) 

and X is defined as above.

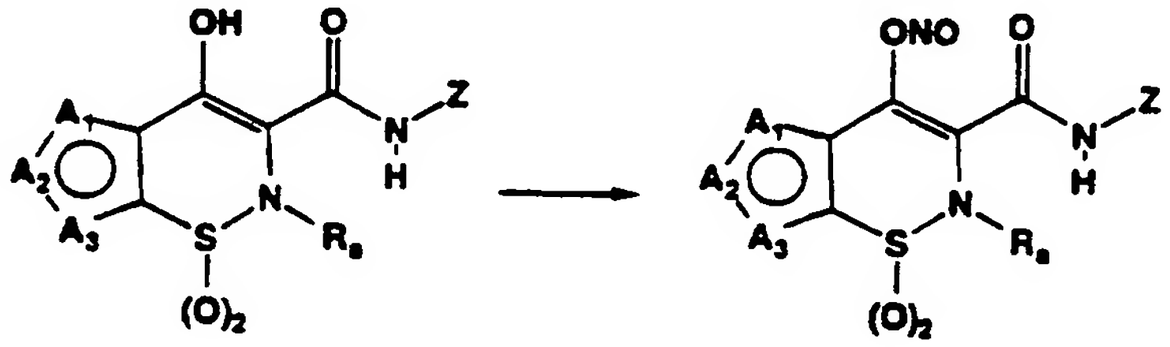
The present invention also relates to processes for preparing the compounds of formula (I), (II), (III) or (IV) and to the intermediates useful in such processes.

Compounds of the present invention may be synthesized as shown in reaction Schemes I through XI presented below, in which R_a, R_b, R_c, R_d, R_e, R_f, R_g, A_1, A_2, A_3, p, and Z are as defined above or as depicted in the reaction schemes for formulas **I**, **II**, **III** or **IV**; P^1 is an oxygen protecting group and P^2 is a sulfur protecting group. The reactions are performed in solvents appropriate to the reagents and materials employed are suitable for the transformations being effected. It is understood by those skilled in the art of organic synthesis that the functionality present in the molecule must be consistent with the chemical transformation proposed. This will, on occasion, necessitate judgment by the routineer as to the order of synthetic steps, protecting groups required, and deprotection conditions. Substituents on the starting materials may be incompatible with some of the reaction conditions required in some of the methods described, but alternative methods and substituents compatible with the reaction conditions will be readily apparent to skilled practitioners in the art. The use of sulfur and oxygen protecting groups is well known in the art for protecting thiol, alcohol, and amino groups against undesirable reactions during a synthetic procedure and many such protecting groups are known, *c.f.*, T.H. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York (1991).

Nitroso compounds of formula (I) wherein A_1, A_2, A_3, R_a, and Z are defined as above and an O-nitrosyated enol is represenatative of the D group as defined

above may be prepared according to reaction Scheme I. The enolic form of the β-keto amide of the formula 1 is reacted with a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite [c.f., Hakimelahi et al., *Helvetica Chimica Acta*, *67*, 907 (1984)], or nitrosium tetrafluoroborate in a suitable anhydrous solvent such as methylene chloride, tetrahydrofuran (THF), dimethylforamide (DMF), or acetonitrile with or without am amine base such as pyridine or triethylamine to afford the O-nitrite **IA**.

Scheme I

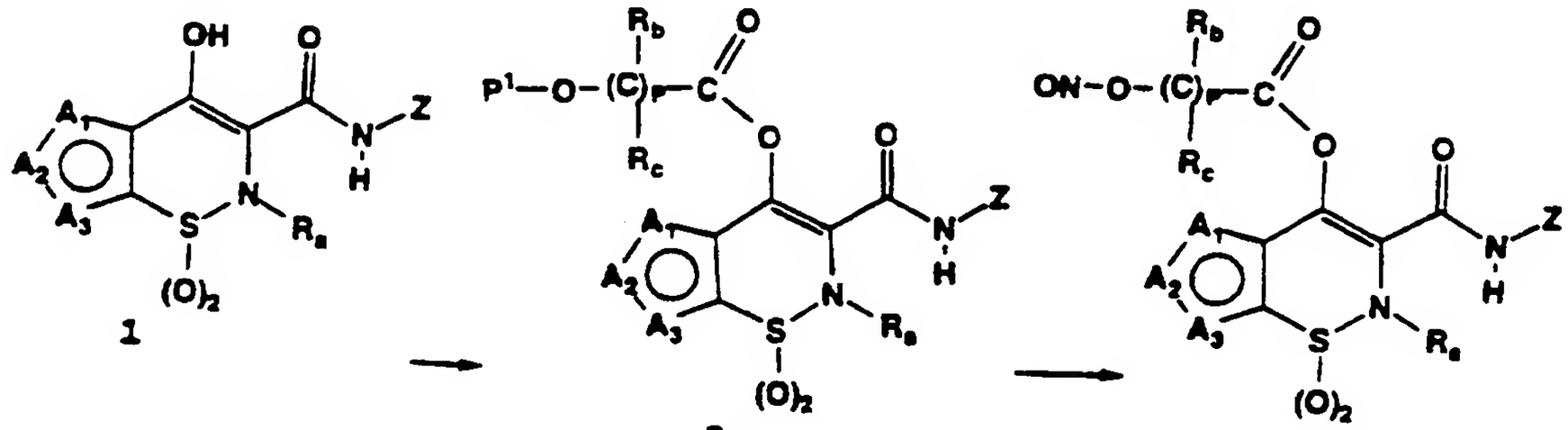


1 IA

Nitroso compounds of formula (I) wherein p, A_1, A_2, A_3, R_a, R_b, R_c, and Z are defined as above and an O-nitrosylated ester is representative of the D group as defined above may be prepared according to Scheme II. The enolic form of the β-keto amide of the formula 1 is converted to the ester of the formula 2 wherein p, R_b and R_c are defined as above by reaction with an appropriate protected alcohol containing activated acylating agent wherein P^1 is as defined above. Preferred methods for the formation of enol ester are reacting the enol with the preformed acid chloride or symmetrical anhydride of the protected alcohol containing acid. Preferred protecting groups for the alcohol moiety are silyl ethers such as a trimethylsilyl or a tert-butyldimethylsilyl ether. Deprotection of the hydroxyl moiety (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction with a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite, or nitrosium tetrafluoroborate in a suitable anhydrous solvent such as dichloromethane,

THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula IB.

Scheme II

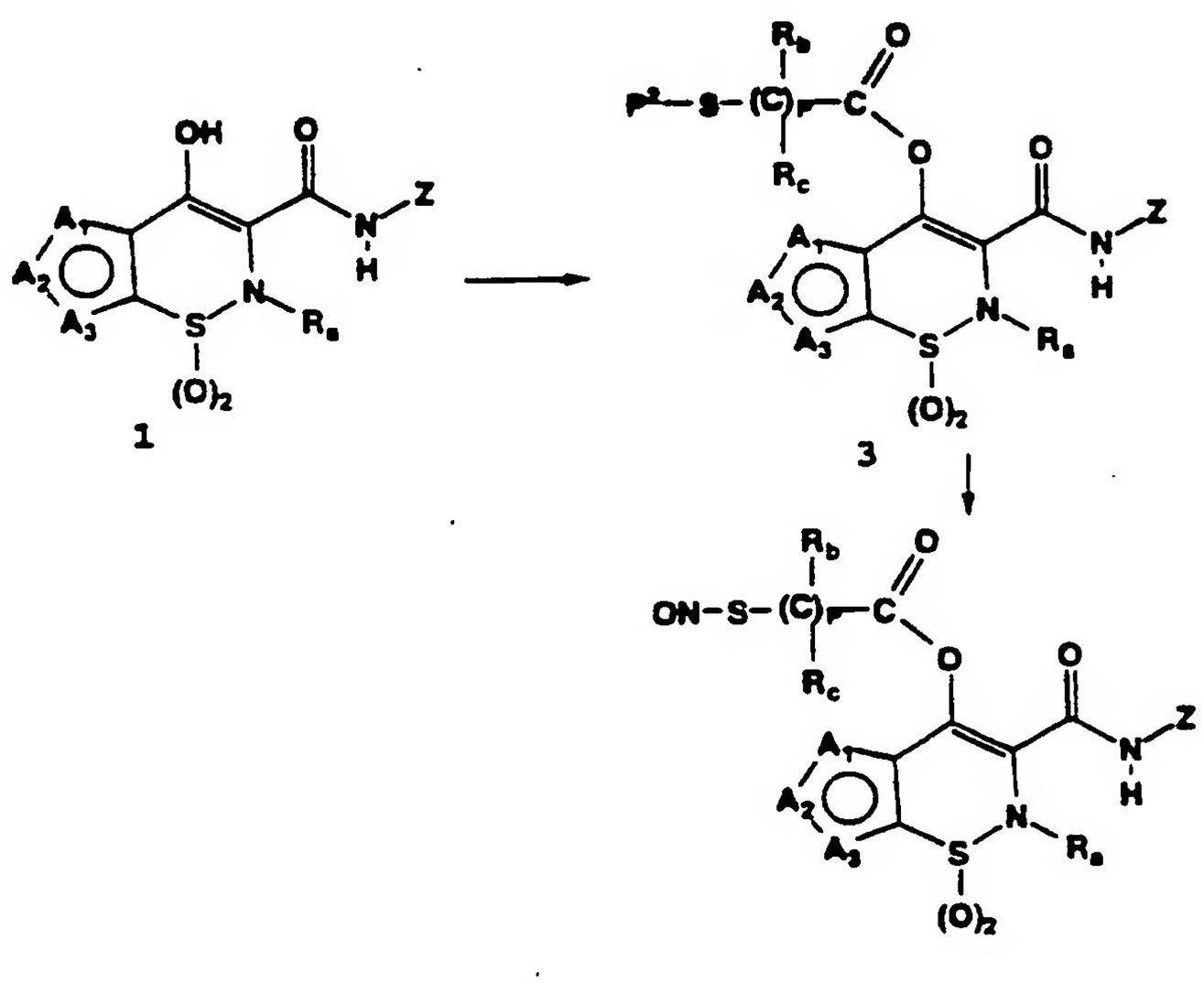


1 2 IB

Nitroso compounds of formula (I) wherein p, A_1, A_2, A_3, R_a, R_b, R_c, and Z are defined as above and an S-nitrosyated enol ester is representative of the D group as defined above may be prepared according to reaction Scheme III. The enolic form of the β-keto amide of the formula 1 is converted to the ester of the formula 3 wherein p, R_b, and R_c are defined as above by reaction with an appropriate protected thiol containing activated acylating agent wherein P^2 is as defined above. Preferred methods for the formation of enol ester are reacting the enol with the preformed acid chloride or symmetrical anhydride of the protected thiol containing acid. Preferred protecting groups for the thiol moiety are as a thioester such as a thioacetate or thiobenzoate, as a disulfide, as a thiocarbamate such as N-methoxymethyl thiocarbamate, or as a thioether such as a paramethoxybenzyl thioether, a tetrahydropyranyl thioether or a S-triphenylmethyl thioether. Deprotection of the thiol moiety (zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are preferred methods for reducing disulfide groups while aqueous base

is typically utilized to hydrolyze thioesters and N-methoxymethyl thiocarbamates and mercuric trifluoroacetate, silver nitrate, or strong acids such as trifluoroacetic or hydrochloric acid and heat are used to remove a paramethoxybenzyl thioether, a tetrahydropyranyl thioether or a S-triphenylmethyl thioether group) followed by reaction with a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite, a lower alkyl nitrite such as tert-butyl nitrite, or nitrosium tetrafluoroborate in a suitable anhydrous solvent such as methyene chloride, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula IC. Alternatively, reacting this intermediate with a stoichiometric quantity of sodium nitrite in aqueous acid affords the compound of the formula IC.

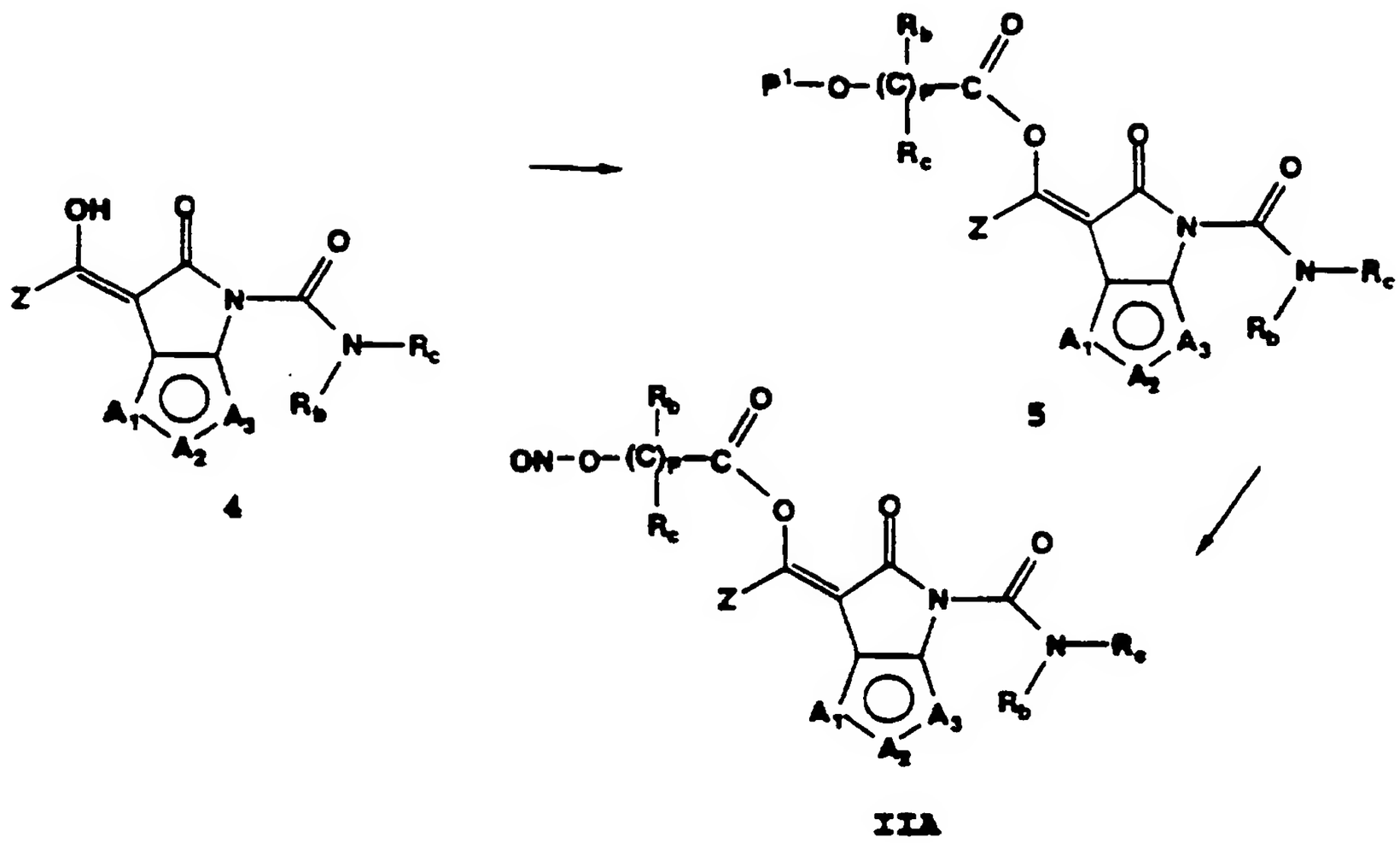
Scheme III



IC

Nitroso compounds of formula (II) wherein p, A_1, A_2, A_3, R_b and R_c, and Z are defined as above and an O-nitrosylated ester is representative of the D group as defined above may be prepared according to Scheme IV. The enolic form of the β-keto amide of the formula **4** is converted to the ester of the formula **5** wherein p, R_b and R_c are defined as above by reaction with an appropriate protected alcohol containing activated acylating agent wherein P^1 is as defined above. Preferred methods for the formation of enol ester are reacting the enol with the preformed acid chloride or symmetrical anhydride of the protected alcohol containing acid. Preferred protecting groups for the alcohol moiety are silyl ethers such as a trimethylsilyl or a tert-butyldimethylsilyl ether. Deprotection of the hydroxyl moiety (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite, or nitrosium tetrafluoroborate in a suitable anhydrous solvent such as dichloromethane, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula **IIA**.

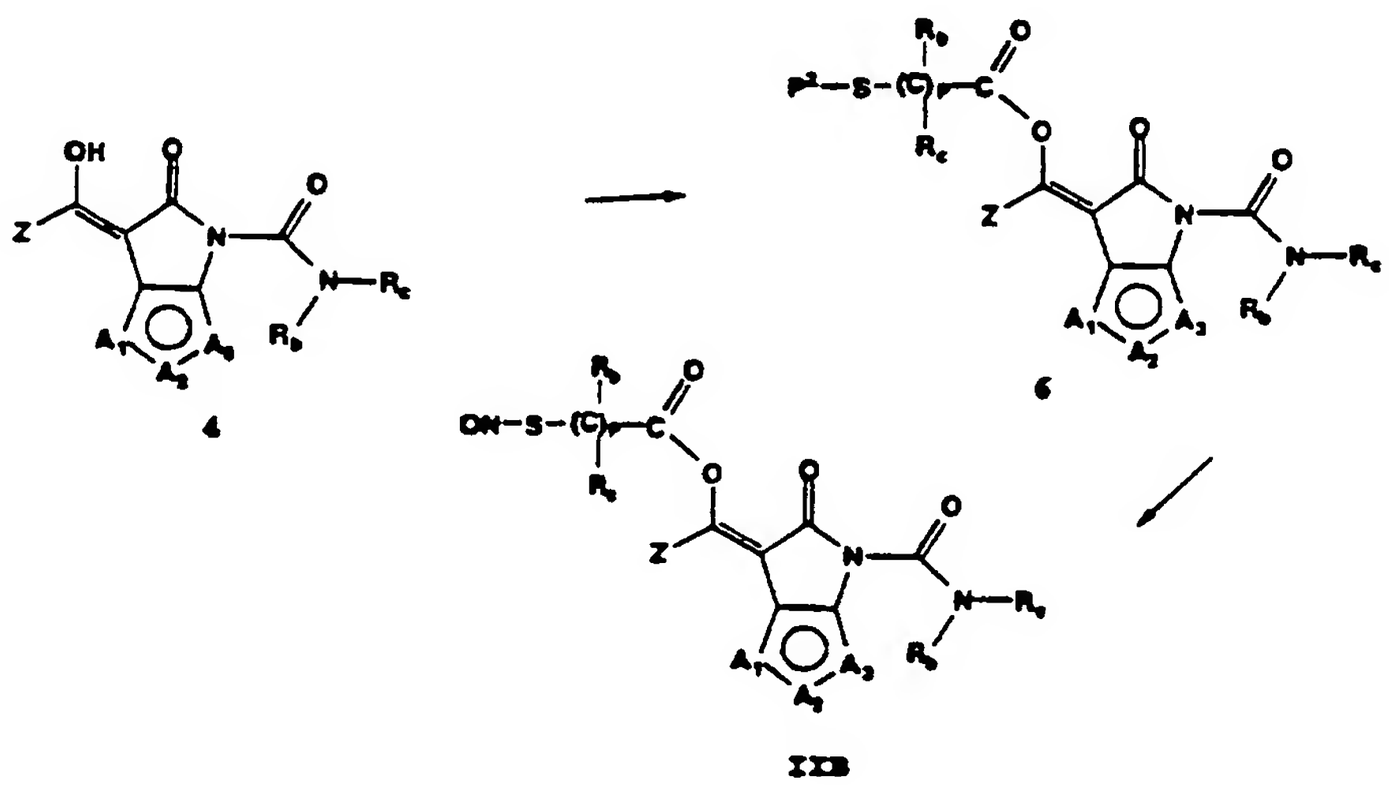
Scheme IV



Nitroso compounds of formula (II) wherein p, A_1, A_2, A_3, R_b, R_c, and Z are defined as above and an S-nitrosyated enol ester is represenatative of the D group as defined above may be prepared according to reaction Scheme V. The enolic form of the β-keto amide of the formula **4** is converted to the ester of the formula **6** wherein p, R_b and R_c are defined as above by reaction with an appropriate protected thiol containing activated acylating agent wherein P^2 is as defined above. Preferred methods for the formation of enol ester are reacting the enol with the preformed acid chloride or symmetrical anhydride of the protected thiol containing acid. Preferred protecting groups for the thiol moiety are as a thioester such as a thioacetate or thiobenzoate, as a disulfide, as a thiocarbamate such as N-methoxymethyl thiocarbamate, or as a thioether such as a paramethoxybenzyl thioether, a tetrahydropyranyl thioether, or a S-triphenylmethyl thioether. Deprotection of the thiol moiety (zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are preferred methods for reducing disulfide groups while aqueous base

is typically utilized to hydrolyze thiolesters and N-methoxymethyl thiocarbamates and mercuric trifluoroacetate, silver nitrate. or strong acids such as trifluoroacetic or hydrochloric acid and heat are used to remove a paramethoxybenzyl thioether. a tetrahydropyranyl thioether or a S-triphenylmethyl thioether group) followed by reaction a suitable nitrosylating agent such as thionyl chloride nitrite. thionyl dinitrite. a lower alkyl nitrite such as tert-butyl nitrite, or nitrosium tetrafluoroborate in a suitable anhydrous solvent such as methyene chloride, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine acid affords the compound of the formula **IIB**. Alternatively, reacting this intermediate with a stiochiometric quantity of sodium nitrite in aqueous acid affords the compound of the formula **IIB**.

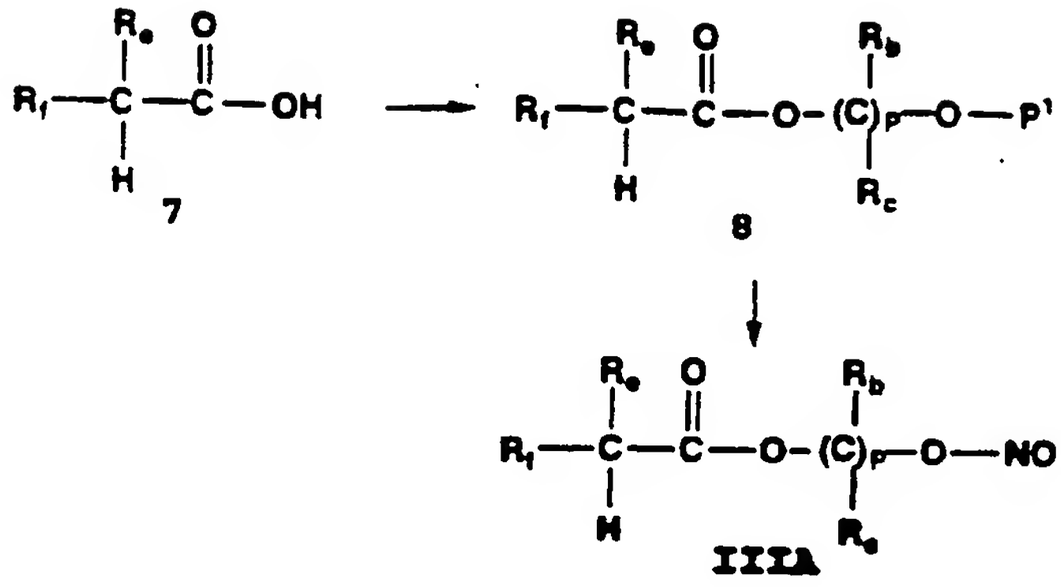
Scheme V



Nitroso compounds of formula **(III)** wherein p, R_b, R_c, R_e and R_f are defined as above and an O-nitrosylated ester is representative of the X group as defined above may be prepared according to Scheme VI. An acid of the formula **7** is converted into the ester of the formula **8** wherein p, R_b and R_c are defined as above by reaction with an appropriate monoprotected diol. Preferred methods for the preparation of esters are initially forming the mixed anhydride via reaction of 7 with a chloroformate

such as isobutylchloroformate in the presence of a non nucleophilic base such as triethylamine in an anhydrous inert solvent such as dichloromethane. diethylether. or THF. The mixed anhydride is then reacted with the monoprotected alcohol preferably in the presence of a condensation catalyst such as 4-dimethylamine pyridine. Alternatively, the acid 7 may be first converted to the acid chloride by treatment with oxalyl chloride in the presence of a catalytic amount of DMF. The acid chloride is then reacted with the monoprotected alcohol preferably in the presence of a condensation catalyst such as 4-dimethylamine pyridine and a tertiary amine base such as triethyl amine to afford the ester 8. Alternatively, the acid 7 and monoprotected diol may be coupled to afford 8 by treatment with a dehydration agent such as 1,3-dicyclohexylcarbodiimide (DCC). Alternatively, compound 7 may be first converted into an alkali metal salt such as the sodium, potassium, or lithium salt. and reacted with an alkyl halide which also contains a protected hydroxyl group in an polar solvent such as DMF to afford 8. Preferred protecting groups for the alcohol moiety are silyl ethers such as a trimethylsilyl or a tert-butyldimethylsilyl ether. Deprotection of the hydroxyl moiety (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction with a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite, or nitrosium tetrafluoroborate in a suitable anhydrous solvent such as dichloromethane, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula **IIIA**.

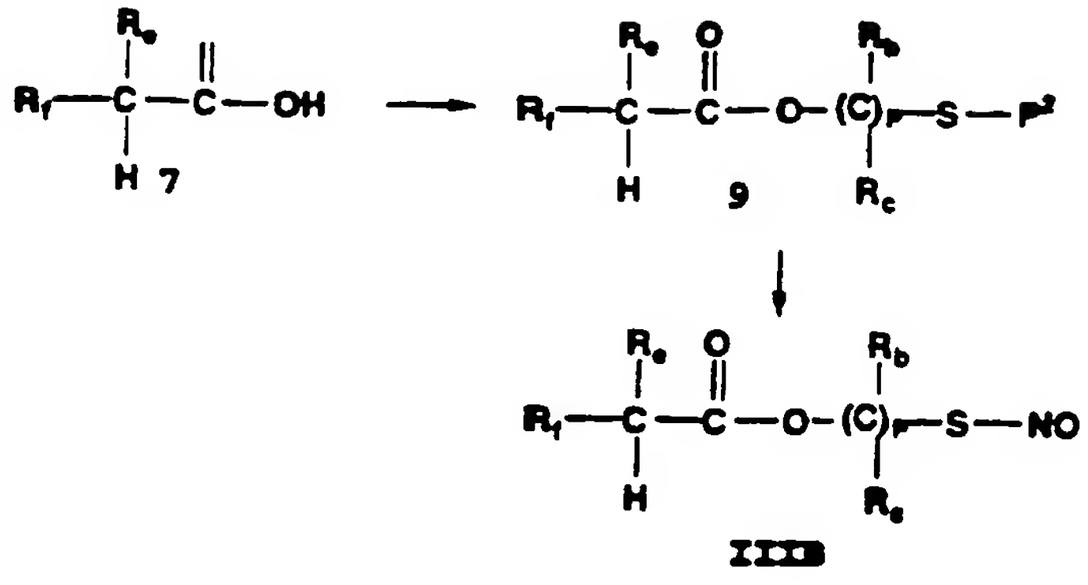
Scheme VI



Nitroso compounds of formula (III) wherein p, R_b, R_c, R_e, and R_f are defined as above and a S-nitrosylated ester is representative of the X group as defined above may be prepared according to Scheme VII. An acid of the formula 7 is converted into the ester of the formula 9 by reaction with an appropriate protected thiol containing alcohol. Preferred methods for the preparation of esters are initially forming the mixed anhydride via reaction of 7 with a chloroformate such as isobutylchloroformate in the presence of a non nucleophilic base such as triethylamine in an anhydrous inert solvent such as diethylether or THF. The mixed anhydride is then reacted with the thiol containing alcohol preferably in the presence of a condensation catalyst such as 4-dimethylamine pyridine. Alternatively, the acid 7 may be first converted to the acid chloride by treatment with oxalyl chloride in the presence of a catalytic amount of DMF. The acid chloride is then reacted with the monoprotected thiol preferably in the presence of a condensation catalyst such as 4-dimethylamine pyridine and a tertiary amine base such as triethyl amine to afford the ester 9. Alternatively, the acid and thiol containing alcohol may be coupled to afford 9 by treatment with a dehydration agent such as DCC. Alternatively, compound 7 may be first converted into an alkali metal salt such as the sodium, potassium, or

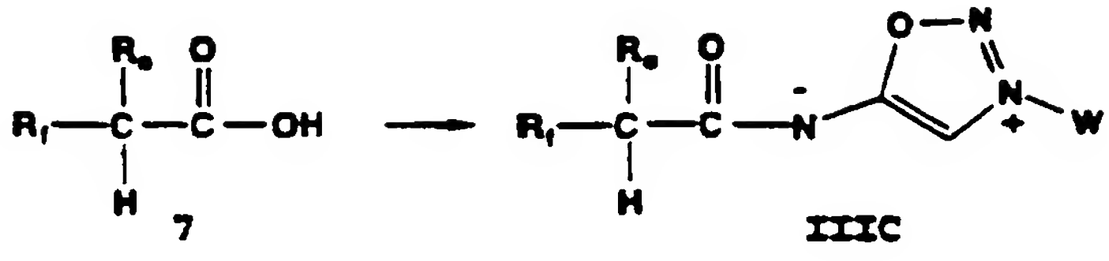
lithium salt, and reacted with an alkyl halide which also contains a protected thiol group in an polar solvent such as DMF to afford **9**. Preferred protecting groups for the thiol moiety are as a thioester such as a thioacetate or thiobenzoate, as a disulfide, as a thiocarbamate such as N-methoxymethyl thiocarbamate, or as a thioether such as a paramethoxybenzyl thioether, a tetrahydropyranyl thioether, or a S-triphenylmethyl thioether. Deprotection of the thiol moiety (zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are preferred methods for reducing disulfide groups while aqueous base is typically utilized to hydrolyze thiolesters and N-methoxymethyl thiocarbamates and mercuric trifluoroacetate, silver nitrate, or strong acids such as trifluoroacetic or hydrochloric acid and heat are used to remove a paramethoxybenzyl thioether, a tetrahydropyranyl thioether or a S-triphenylmethyl thioether group) followed by reaction with a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite, a lower alkyl nitrite such as tert-butyl nitrite, or nitrosium tetrafluoroborate in a suitable anhydrous solvent such as methylene chloride, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula **IIIB**. Alternatively, this intermediate may be reacted with a stoichiometric quantity of sodium nitrite in aqueous acid affords the compound of the formula **IIIB**.

Scheme VII



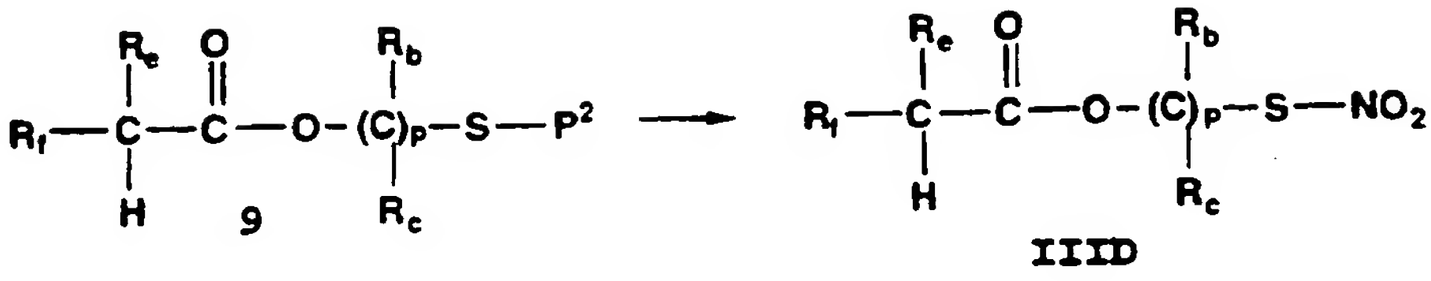
Nitroso compounds of formula (**III**) wherein W, R_e, and R_f are defined as above and a 6-W-substituted sydnonimine wherein W is as defined above is representative of the X group as defined above may be prepared according to Scheme VIII. An acid of the formula 7 is converted into the carboximide of the formula **IIIC** by reaction with a 6-W-substituted sydnonimine. Preferred methods for the preparation of carboximides are initially forming the mixed anhydride via reaction of 7 with a chloroformate such as isobutylchloroformate in the presence of a non nucleophilic base such as triethylamine in an anhydrous inert solvent such as diethylether or THF. The mixed anhydride is then reacted with the 6-W-substituted sydnonimine to afford **IIIC**. Alternatively, the acid 7 may be coupled to the 6-W-substituted sydnonimine to afford **IIIC** by treatment with a dehydration agent such as DCC. Alternatively, the acid 7 may be converted into an active ester by reaction with a suitably substituted phenol utilizing any of the conditions for ester formation described for Scheme VI, followed by reaction with a 6-W-substituted sydnonimine. Preferred 6-W-substituted sydnonimines are 1,2,6,4-oxatriazolium, 6-amino-6-morpholine and 1,2,6,4-oxatriazolium, 6-amino-6-(6-chloro-2-methyl -benzene) and preferred active esters are para-nitrophenyl, 2,4,5-trichlorophenyl, and pentafluorophenyl.

Scheme VIII



Nitroso compounds of formula (**III**) wherein p, R_b, R_c, R_e, and R_f are defined as above and a S-nitrosated ester is representative of the X group as defined above may be prepared according to Scheme IX. The protected thiol containing ester of the formula **9** is deprotected. Zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are preferred methods for reducing disulfide groups while aqueous base is typically utilized to hydrolyze thiolesters and N-methoxymethyl thiocarbamates and mercuric trifluoroacetate, silver nitrate, or strong acids such as trifluoroacetic or hydrochloric acid and heat are used to remove a paramethoxybenzyl thioether, a tetrahydropyranyl thioether or a S-triphenylmethyl thioether group. Reaction of the thiol group(s) excess dinitrogen tetroxide in a solvent such as methylene chloride, THF, DMF, or acetonitrile affords the compound of the formula **IIID**.

Scheme IX

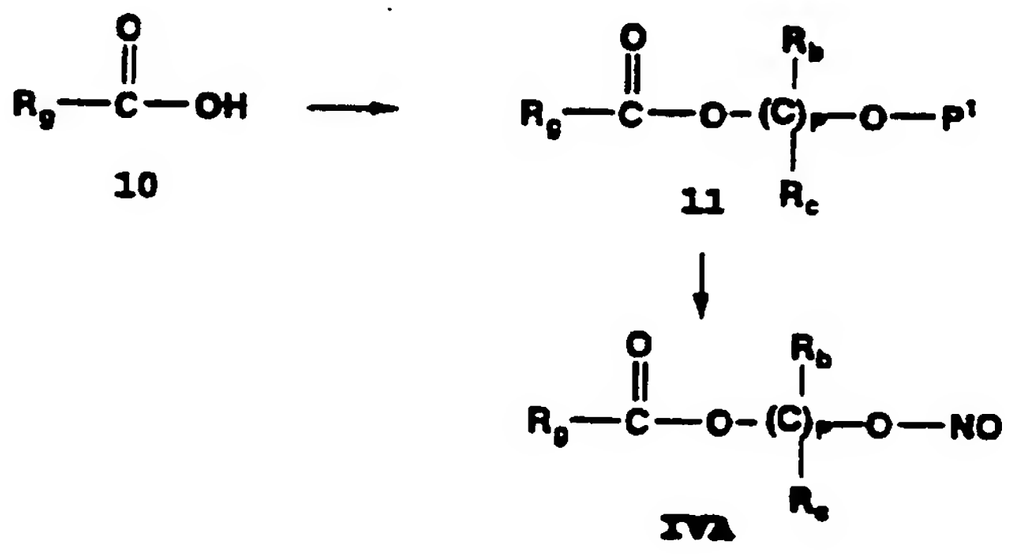


IIID

Nitroso compounds of formula (**IV**) wherein p, R_b, R_c, and R_g are defined as above and an O-nitrosylated ester is representative of the X group as defined above may be prepared according to Scheme IX. An acid of the formula **10** is converted into the ester of the formula **11** wherein p, R_b, and R_c are defined as above, by reaction with an appropriate monoprotected diol. Preferred methods for the preparation of esters are initially forming the mixed anhydride via reaction of **10** with a chloroformate such as isobutylchloroformate in the presence of a non nucleophilic base such as triethylamine in an anhydrous inert solvent such as dichloromethane, diethylether or THF. The mixed anhydride is then reacted with the monoprotected alcohol preferably in the presence of a condensation catalyst such as 4-dimethylamine pyridine. Alternatively, the acid **10** may be first converted to the acid chloride by treatment with oxalyl chloride in the presence of a catalytic amount of DMF. The acid chloride is then reacted with the monoprotected alcohol preferably in the presence of a condensation catalyst such as 4-dimethylamine pyridine and a tertiary amine base such as triethylamine to afford the ester **11**. Alternatively, the acid **10** and monoprotected diol may be coupled to afford **11** by treatment with a dehydration agent such as DCC. Alternatively, compound **10** may be first converted into an alkali metal salt such as the sodium, potassium, or lithium salt, which is then reacted with an alkyl halide which also contains a protected hydroxyl group in an polar solvent

such as DMF to afford **11**. Preferred protecting groups for the alcohol moiety are silyl ethers such as a trimethylsilyl or a tert-butyldimethylsilyl ether. Deprotection of the hydroxyl moiety (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction with a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite, or nitrosium tetrafluoroborate in a suitable anhydrous solvent such as methylene chloride, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethyl amine affords the compound of the formula **IVA**.

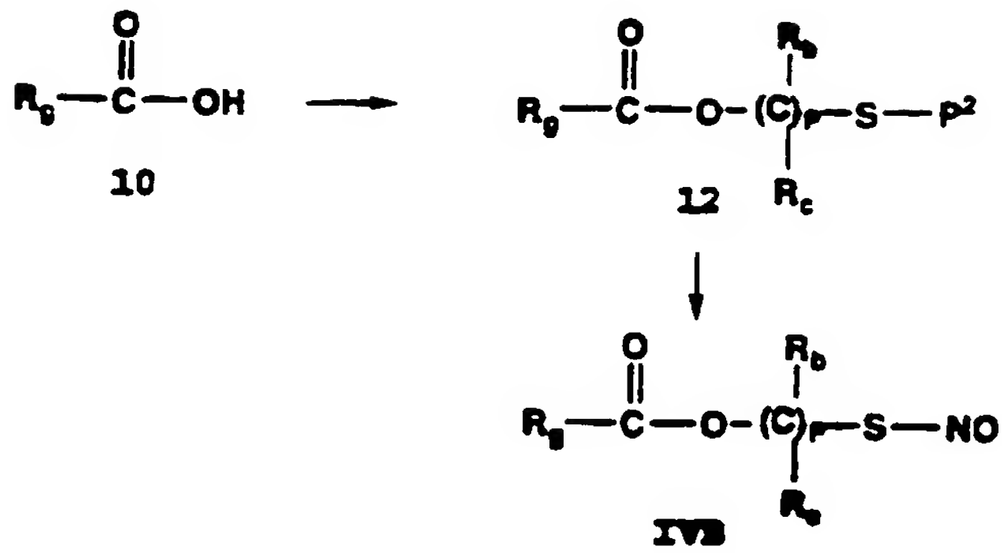
Scheme X



Nitroso compounds of formula (**IV**) wherein R_c is defined as above and a S-nitrosylated ester is representative of the X group as defined above may be prepared according to Scheme X. An acid of the formula **10** is converted into the ester of the formula **12** by reaction with an appropriate protected thiol containing alcohol. Preferred methods for the preparation of esters are initially forming the mixed anhydride via reaction of **10** with a chloroformate such as isobutylchloroformate in the presence of a non nucleophilic base such as triethylamine in an anhydrous inert solvent such as diethylether or THF. The mixed anhydride is then reacted with the

protected thiol containing alcohol preferably in the presence of a condensation catalyst such as 4-dimethylaminopyridine. Alternatively, the acid **10** may be first converted to the acid chloride by treatment with oxalyl chloride in the presence of a catalytic amount of DMF. The acid chloride is then reacted with the protected thiol containing alcohol preferably in the presence of a condensation catalyst such as 4-dimethylamineo pyridine and a tertiary amine base such as triethyl amine to afford the ester **12**. Alternatively, the acid and protected thiol containing alcohol may be coupled to afford **12** by treatment with a dehydration agent such as DCC. Alternatively, compound **10** may be first converted into an alkali metal salt such as the sodium, potassium, or lithium salt, which is then reacted with an alkyl halide which also contains a protected thiol group in an polar solvent such as DMF to afford **12** . Preferred protecting groups for the thiol moiety are as a thioester such as a thioacetate or thiobenzoate, as a disulfide, as a thiocarbamate such as N-methoxymethyl thiocarbamate, or as a thioether such as a paramethoxybenzyl thioether, a tetrahydropyranyl thioether, or a S-triphenylmethyl thioether. Deprotection of the thiol moiety (zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are preferred methods for reducing disulfide groups while aqueous base is typically utilized to hydrolyze thiolesters and N-methoxymethyl thiocarbamates and mercuric trifluoroacetate, silver nitrate, or strong acids such as trifluoroacetic or hydrochloric acid and heat are used to remove a paramethoxybenzyl thioether, a tetrahydropyranyl thioether or a S-triphenylmethyl thioether group) followed by reaction with a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite, a lower alkyl nitrite such as tert-butyl nitrite, or nitrosium tetrafluoroborate in a suitable anhydrous solvent such as methylene chloride, THF, DMF, or acetonitrile affords the compound of the formula **IVB**. Alternatively, this intermediate may be reacted with a stoichiometric quantity of sodium nitrite in aqueous acid affords the compound of the formula **IVB**

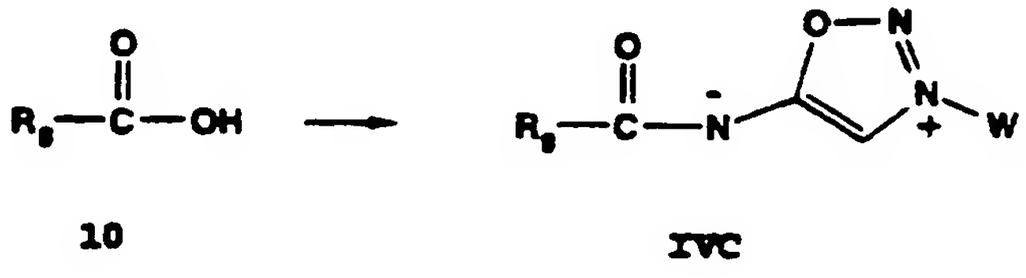
Scheme XI



Nitroso compounds of formula (IV) wherein R_g is defined as above and a 6-substituted sydnonimine is representative of the X group as defined above may be prepared according to Scheme XI. An acid of the formula **10** is converted into the carboximide of the formula IVC by reaction with a 6-W-substituted sydnonimine wherein W is as defined above. Preferred methods for the preparation of carboximides are initially forming the mixed anhydride via reaction of **10** with a chloroformate such as isobutylchloroformate in the presence of a non nucleophilic base such as triethylamine in an anhydrous inert solvent such as diethylether or THF. The mixed anhydride is then reacted with the 6-W-substituted sydnonimine to afford **IVC**. Alternatively, the acid **10** may be coupled to the 6-W-substituted sydnonimine afford **IVC** by treatment with a dehydration agent such as DCC. Alternatively, the acid **10** may be converted into an active ester by reaction with a suitably substituted phenol utilizing any of the conditions for ester formation described above, followed by reaction with a 6-W-substituted sydnonimine. Preferred 6-W-substituted sydnonimines are 1,2,6,4-oxatriazolium, 6-amino-6-morpholine and 1,2,6,4-

oxatriazolium. 6-amino-6-(6-chloro-2-methyl -benzene) and preferred active esters are para-nitrophenyl. 2.4,5-trichlorophenyl. and pentafluorophenyl.

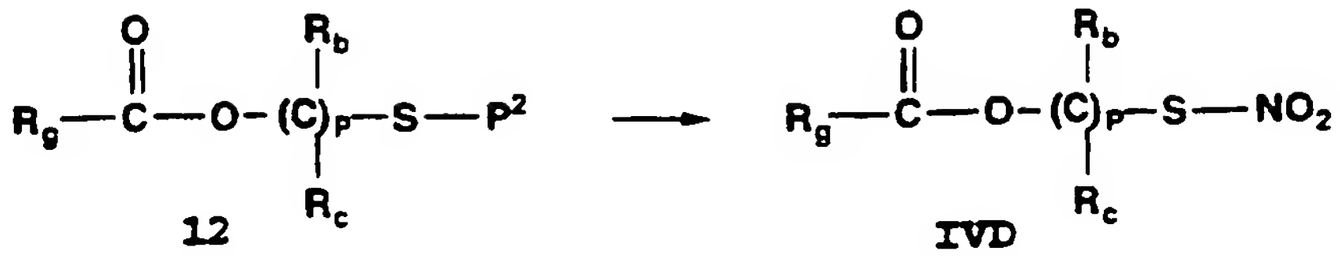
Scheme XII



10 IVC

Nitroso compounds of formula (IV) wherein p, R_b, R_c, and R_g are defined as above and a S-nitrosated ester is representative of the X group as defined above may be prepared according to Scheme XIII. The protected thiol containing ester of the formula **12** is deprotected. Zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are preferred methods for reducing disulfide groups while aqueous base is typically utilized to hydrolyze thiolesters and N-methoxymethyl thiocarbamates and mercuric trifluoroacetate, silver nitrate, or strong acids such as trifluoroacetic or hydrochloric acid and heat are used to remove a paramethoxybenzyl thioether, a tetrahydropyranyl thioether or a S-triphenylmethyl thioether group. Reaction of the thiol group(s) with excess dinitrogen tetroxide in a solvent such as methylene chloride, THF, DMF, or acetonitrile affords the compound of the formula **IVD**.

Scheme XIII



The compounds that donate, transfer or release nitric oxide can be any of those known to the art, including those mentioned and/or exemplified below.

Nitrogen monoxide can exist in three forms: NO^- (nitroxyl), NO• (nitric oxide) and NO^+ (nitrosonium). NO• is a highly reactive short-lived species that is potentially toxic to cells. This is critical, because the pharmacological efficacy of NO depends upon the form in which it is delivered. In contrast to nitric oxide radical, nitrosonium and nitroxyl do not react with O_2 or O_2^-• species, and are also resistant to decomposition in the presence of redox metals. Consequently, administration of NO equivalents does not result in the generation of toxic by-products or the elimination of the active NO moiety.

Compounds contemplated for use in the invention are nitric oxide and compounds that release nitric oxide or otherwise directly or indirectly deliver or transfer nitric oxide to a site of its activity, such as on a cell membrane, *in vivo*. As used here, the term "nitric oxide" encompasses uncharged nitric oxide (NO•) and charged nitric oxide species, particularly including nitrosonium ion (NO^+) and nitroxyl ion (NO^-). The reactive form of nitric oxide can be provided by gaseous nitric oxide. The nitric oxide releasing, delivering or transferring compounds, having the structure F-NO_v, wherein F is a nitric oxide releasing, delivering or transferring moiety and v is an integer of 1 or 2, include any and all such compounds which provide nitric oxide

to its intended site of action in a form active for their intended purpose. As used here, the term "NO adducts" encompasses any of such nitric oxide releasing, delivering or transferring compounds, including, for example, S-nitrosothiols, S-nitroso amino acids, S-nitroso-polypeptides, organic nitrites and organic thionitrates. It is contemplated that any or all of these "NO adducts" can be mono- or poly-nitrosylated and/or nitrosated at a variety of naturally susceptible or artificially provided binding sites for nitric oxide.

One group of such NO adducts is the S-nitrosothiols, which are compounds that include at least one -S-NO group. Such compounds include S-nitroso-polypeptides (the term "polypeptide" includes proteins and also polyamino acids that do not possess an ascertained biological function, and derivatives thereof); S-nitrosylated amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures and derivatives thereof); S-nitrosylated sugars, S-nitrosylated-modified and unmodified oligonucleotides (preferably of at least 5, and more particularly 5-200, nucleotides); and an S-nitrosylated hydrocarbon where the hydrocarbon can be a branched or unbranched, and saturated or unsaturated aliphatic hydrocarbon, or an aromatic hydrocarbon; S-nitroso hydrocarbons having one or more substituent groups in addition to the S-nitroso group; and heterocyclic compounds. S-nitrosothiols and the methods for preparing them are described in U.S. Patent Application No. 07/943.834, filed September 14, 1992, Oae *et al.*, *Org. Prep. Proc. Int.*, *15*(3):165-198 (1983); Loscalzo *et al.*, *J. Pharmacol. Exp. Ther.*, *249*(3):726-729 (1989) and Kowaluk *et al.*, *J. Pharmacol. Exp. Ther.*, *256*:1256-1264 (1990), all of which are incorporated in their entirety by reference.

One particularly preferred embodiment of this aspect relates to S-nitroso amino acids where the nitroso group is linked to a sulfur group of a sulfur-containing amino acid or derivative thereof. For example, such compounds include the following: S-nitroso-N-acetylcysteine, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine and S-nitroso-glutathione.

Suitable S-nitrosylated proteins include thiol-containing proteins (where the NO group is attached to one or more sulfur group on an amino acid or amino acid derivative thereof) from various functional classes including enzymes. such as tissue-type plasminogen activator(TPA) and cathepsin B; transport proteins. such as lipoproteins, heme proteins such as hemoglobin and serum albumin: and biologically protective proteins, such as the immunoglobulins and the cytokines. Such nitrosylated proteins are described in PCT Publ. Applic. No. WO 93/09806, published May 27, 1993. Examples include polynitrosylated albumin where multiple thiol or other nucleophilic centers in the protein are modified.

Further examples of suitable S-nitrosothiols include those having the structures:

(i) $CH3[C(R_b)(R_c)]_xSNO$

wherein x equals 2 to 20 and R_b and R_c are as defined above;

(ii) $HS[C(R_b)(R_c)]_xSNO$

wherein x equals 2 to 20; and

(iii) $ONS[C(R_b)(R_c)]_xV$

wherein x equals 2 to 20 and V is selected from the group consisting of fluoro, alkoxy, cyano, carboxamido, cycloalkyl, arylkoxy. alkylsulfinyl, arylthio, alkylamino, dialkylamino, hydroxy, carbamoyl, N-alkylcarbamoyl, N,N-dialkylcarbamoyl. amino, hydroxyl, carboxyl, hydrogen. nitro and aryl; and x, R_b and R_c are as defined above.

Nitrosothiols can be prepared by various methods of synthesis. In general, the thiol precursor is prepared first, then converted to the S-nitrosothiol derivative by nitrosation of the thiol group with $NaNO_2$ under acidic conditions (pH is about 2.5) which yields the S-nitroso derivative. Acids which may be used for this purpose include aqueous sulfuric, acetic and hydrochloric acids. Alternatively, they may be

nitrosated by reaction with an organic nitrite such as tert-butyl nitrite, or an nitrosonium salt such as nitrosonium tetraflurorborate in an inert solvent.

Another group of such NO adducts are those wherein the compounds donate, transfer or release nitric oxide and are selected from the group consisting of compounds that include at least one ON-O-, ON-N- or ON-C- group. The compound that includes at least one ON-O-, ON-N- or ON-C- group is preferably selected from the group consisting of ON-O-,ON-N- or ON-C-polypeptides (the term "polypeptide" includes proteins and also polyamino acids that do not possess an ascertained biological function, and derivatives thereof); ON-O-, ON-N- or ON-C-amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures); ON-O-, ON-N- or ON-C-sugars; ON-O-, ON-N- or ON-C-modified and unmodified oligonucleotides (preferably of at least 5, and more particularly 5-200, nucleotides), ON-O-, ON-N- or ON-C-hydrocarbons which can be branched or unbranched, saturated or unsaturated aliphatic hydrocarbons or aromatic hydrocarbons; ON-O-, ON-N- or ON-C- hydrocarbons having one or more substituent groups in addition to the ON-O-, ON-N- or ON-C- group; and ON-O-, ON-N- or ON-C-heterocyclic compounds.

Another group of such adducts are 2-hydroxy-2-nitrosohydrazines which donate, transfer or release nitric oxide and have a $R_{100}R_{200}$-N(O^-M^+)-NO group wherein R_{100} and R_{200} include polypeptides, amino acids, sugars, modified and unmodified oligonucleotides, hydrocarbons where the hydrocarbon can be a branched or unbranched, and saturated or unsaturated aliphatic hydrocarbon or an aromatic hydrocarbon, hydrocarbons having one or more substituent groups and heterocyclic compounds. M^+ is a metal cation, such as, for example, a Group I metal cation.

Another group of such adducts are thionitrates which donate, transfer or release nitric oxide and have the structure R_{100}-(S)-NO_2 wherein R_{100} is as described

above for the N-oxo-N-nitrosoamines. Particularly preferred are those compounds where R_{100} is a polypeptide or hydrocarbon.

Agents which stimulate endogenous NO synthesis such as L-arginine. the substrate for nitric oxide synthase, are also suitable for use in accordance with the invention.

When administered *in vivo*, the compositions may be administered in combination with pharmaceutical carriers and in dosages described herein.

The compositions of the present invention may be administered orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers. adjuvants. and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, granules and gels. In such solid dosage forms, the active compounds may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert diluents, *e.g.*, lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Dosage forms for topical administration of the composition can include creams, sprays, lotions, gels, ointments and the like. In such dosage forms the compositions of the invention can be mixed to form white, smooth. homogeneous. opaque lotions with, for example, benzyl alcohol 1% (wt/wt) as preservative,

emulsifying wax, glycerin, isopropyl palmitate, lactic acid. purified water. sorbitol solution and polyethylene glycol 400. They can be mixed to form a white, smooth. homogeneous, opaque creams with, for example, benzyl alcohol 2% (wt/wt) as preservative, emulsifying wax, glycerin, isopropyl palmitate, lactic acid, purified water, and sorbitol solution. They can be mixed to form ointments with. for example, benzyl alcohol 2% (wt/wt) as preservative, white petrolatum. emulsifying wax, and tenox II (butylated hydroxyanisole, propyl gallate. citric acid, propylene glycol). Woven pads or rolls of bandaging material, e.g. gauge, can be impregnated with the compositions in solution, lotion, cream. ointment or other such form can also be used for topical application. The compositions can also be applied topically using a transdermal system, such as one of an acrylic-based polymer, adhesive with a resinous crosslinking agent impregnated with the composition and laminated to an impermeable backing.

Suppositories for rectal administration of the drug composition, such as for treating pediatric fever *etc*., can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1, 3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition. sterile, fixed oils are conventionally employed an a solvent or suspending medium.

While the compositions of the invention can be administered as a mixture of an NSAID and a nitric oxide donor, they can also be used in combination with one or more additional compounds which are known to be effective against the specific disease state that one is targeting for treatment.

The compositions of this invention can further include conventional excipients, *i. e.*, pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral application which do not deleteriously react with the active compounds. Suitable pharmaceutically acceptable carriers include, but are not limited to, water, salt solutions, alcohol, vegetable oils, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, petroethral fatty acid esters, hydroxymethylcellulose, polyvinylpyrrolidone, *etc*. The pharmaceutical preparations can be sterilized and if desired, mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, colorings, flavoring and/or aromatic substances and the like which do not deleteriously react with the active compounds. For parenteral application, particularly suitable vehicles consist of solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants. Aqueous suspensions may contain substances which increase the viscosity of the suspension and include, for example, sodium carboxymethyl cellulose, sorbitol and/or dextran. Optionally, the suspension may also contain stabilizers.

The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. The composition can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulations can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, *etc*.

Various delivery systems are known and can be used to administer a therapeutic compound or composition of the invention, *e.g.*, encapsulation in liposomes, microparticles, microcapsules and the like.

The therapeutics of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include, but are not limited to, those formed with free amino groups such as those derived from hydrochloric, phosphoric, sulfuric, acetic, oxalic, tartaric acids, *etc.*, and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, *etc.*

The term "therapeutically effective amount," for the purposes of the invention, refers to the amount of the nitric oxide adduct which is effective to achieve its intended purpose. While individual needs vary, determination of optimal ranges for effective amounts of each nitric oxide adduct is within the skill of the art. Generally, the dosage required to provide an effective amount of the composition, and which can be adjusted by one of ordinary skill in the art will vary, depending on the age, health, physical condition, sex, weight, extent of disease of the recipient, frequency of treatment and the nature and scope of the disorder.

The amount of a given NSAID which will be effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. Reference is again made to Goodman and Gilman, *supra*; The Physician's Desk Reference, Medical Economics Company, Inc., Oradell, N.J., 1995; and to Drug Facts and Comparisons, Facts and Comparisons, Inc., St. Louis, MO, 1993. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances.

The amount of nitric oxide donor in a pharmaceutical composition may be in amounts of 0.1-10 times the molar equivalent of the NSAID. The usual daily doses of NSAIDs are 3-40 mg/kg body weight and the doses of nitric oxide donors in the pharmaceutical composition may be in amounts of 1-500 mg/kg body weight daily and more usually about 1-50 mg/kg. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems and are in the same ranges or less than as described for the commercially available compounds in the Physician's Desk Reference, *supra*.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

The following non-limitative examples further describe and enable one of ordinary skill in the art to make and use the invention. Flash chromatography was performed on 40 micron silica gel (Baker).

Example 1

Cholest-5-en-3β-O-nitroso alcohol

Cholesterol (0.242 g, 0.62 mmol) was dissolved in anhydrous methylene chloride (3 mL) and pyridine (0.103 g, 3.45 mmol) was added, followed by nitrosonium tetrafluoroborate (0.036 g, 0.31 mmol). After stirring for 1 hour at room temperature, an additional nitrosonium tetrafluoroborate (0.099 g, 0.85 mmol) was added. The reaction mixture was stirred at room temperature for 16 hours. The solvent was evaporated and the residue was purified by flash chromatography on silica gel, deactivated with

triethylamine, eluted methylene chloride to give 0.165 g (64 % yield) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz), δ 0.86 (d, 6 H), 0.92 (d, 3 H), 1.05-1.75 (m, 21 H), 1.80-2.01 (m, 6 H), 2.25-2.47 (m, 2 H), 5.23 (m, 1 H), 5 44 (m, 1 H).

Example 2

N-(N-L-γ-glutamyl- S-Nitroso-L-cysteinyl)glycine

N-(N-L-γ-glutamyl-L-cysteinyl)glycine (100 g, 0.325 mol) was dissolved in deoxygenated water (200 ml) and 2N HCl (162 ml) at room temperature and then the reaction mixture was cooled to 0 °C. With rapid stirring, a solution of sodium nitrite (24.4 g, 0.35 mol) in water (40 ml) was added and stirring with cooling of the reaction mixture was continued for approximately 1 hour after which time the pink precipitate which formed was collected by vacuum filtration. The filter cake was resuspended in chilled 40% acetone-water (600 ml) and collected by vacumm filtration. The filter cake was washed with acetone (2 X 200 ml) and ether (100 ml) and then dried under high vacuum at room temperature in the dark to afford the title compound as a pink powder. ^{1}H NMR (D_2O) δ:1.98 (m, 2 H), 2.32 (t,2 H), 3.67 (t, 1 H), 3.82 (s 2 H), 3.86 (dd, 1 H), 3.98 (dd, 1 H), 4.53 (m, 1H).

Example 3

S-Nitroso-triphenylmethanethiol

Triphenylmethyl mercaptan (0.050g, 0.18 mmol) was dissolved in anhydrous methylene chloride and cooled to 0°C. Tert-butyl nitrite (0.186 g, 1.80 mmol) was added and the resulting mixture was stirred at 0°C for 30 minutes. The reaction mixture was allowed to warm to room temperature and stirred at room temperature for 1 hour. The solvent and excess of tert-butyl nitrite were evaporated to give the title compound as a green solid (0.054 g, 98 %). ^{1}H NMR ($CDCl_3$) δ: 7.13-7.18 (m, 4 H), 7.25-7.39 (m, 11 H).

Example 4

4-O-Nitroso-1-(3-benzoyl-α-methylbenzeneacetic acid) butyl ester

4a. 4-Hydroxy-1-(3-benzoyl-α-methylbenzeneacetic acid) butyl ester

3-Benzoyl-α-methylbenzeneacetic acid (4 g, 16 mmol) and 100 μL DMF were dissolved in benzene (25 mL). Oxalyl chloride (1.6 mL, 18 mmol) was added dropwise. Stirring was continued for 2 hour before concentration to a syrup. Butanediol (9 mL, 100 mmol) and pyridine (1.67 mL, 21 mmol) were dissolved in methylene chloride (100 mL) and dioxane (15 mL) and cooled to 0°C. A solution of the acid chloride was added in methylene chloride (20 mL). The reaction mixture was stirred cold for 20 minutes then warmed to room temperature with stirring for 2 hour. The solution was washed 1 X 30 H_2O, 1 N HCl, satd $NaHCO_3$ and brine; dried over Na_2SO_4; and the volatiles were evaporated. The residue was filtered through a pad of silica gel eluting with 2:1 Hex:EtOAc to yield 4.8 g (91 %) of hydroxy ester. ^1H NMR ($CDCl_3$): d 7.41-7.81 (mult, 9 H), 4.08-4.15 (mult, 2 H), 3.79 (q, J = 7.2 Hz, 1 H), 3.59 (t, J = 6.3 Hz, 2 H), 1.53-1.69 (mult, 4 H), 1.53 (d, J = 7.2 Hz, 3H).

4b. 4-O-Nitroso-1-(3-benzoyl-α-methylbenzeneacetic acid) butyl ester

The product of Example 4a (1 g, 3.6 mmol) and pyridine (1.4 mL, 18 mmol) were dissolved in dichloromethane (15 mL) and cooled to -78°C. Nitrosonium tetrafluoroborate (840 mg, 7.2 mmol) was added and the solution was kept cold for 30 minutes. The reaction was warmed to room temperature with continued stirring for 1 hour. The mixture was diluted with dichloromethane and washed with 1N HCl, then brine. The solution was dried over sodium sulfate and evaporated. Chromatography on silica gel eluting with 9:1 Hexane:EtOAc gave 840 mg (76%) of the title compound. ^1H NMR ($CDCl_3$): δ 7.41-7.80 (m, 9 H), 4.65 (m, 1 H), 4.11 (t, J = 6.0 Hz, 2 H), 3.79 (q, J = 7.2 Hz, 1 H), 1.65-1.72 (m, 4 H), 1.53 (d, J = 7.2 Hz, 3H). Anal Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 66.72; H, 5.95; N, 2.93

Example 5

4-O-Nitroso-4-methyl-1-(3-benzoyl-α-methylbenzeneacetic acid) pentyl ester

5a. 4-Hydroxy-4-methyl-1-(3-benzoyl-α-methylbenzeneacetic acid) pentyl ester

3-Benzoyl-α-methylbenzeneacetic acid (1.99 g, 7.7 mmol) in methylene chloride (20 mL) under nitrogen and cooled over ice was treated successively with oxalyl chloride (1.36 mL, 15.7 mmol) and dimethylformamide (5 drops). A vigorous gas evolution was noted and the reaction mixture was stirred with slow warming and then overnight at ambient temperature. The volatile materials were removed *in vacuo* and the residue dissolved in methylene chloride (10 mL) and added dropwise to a precooled mixture of 2-methyl-2,5-pentanediol (3.7 g, 31 mmol) and pyridine (0.69 mL, 8.6 mmol) also in methylene chloride (10 mL) under a nitrogen atmosphere. The reaction mixture was stirred under nitrogen with slow warming and then overnight at ambient temperature. The solution was washed successively with 2N hydrochloric acid and 2N sodium hydroxide, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual oil was subjected to column chromatography using ethyl acetate/hexane (1:2). The product was isolated as an oil in 76% yield (2.1 g). ^{1}H NMR ($CDCl_3$) δ: 7.77-7.81 (m, 3 H), 7.64-7.43 (m, 6 H), 4.18-4.03 (m, 2 H), 3.80 (q, J=7.2 Hz, 1 H), 1.62-1.71 (m, 2 H), 1.54 (d, J=7.2 Hz, 3 H), 1.42-1.35 (m, 2 H), 1.16 (s, 6H). Anal calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.26; H, 7.43.

5b. 4-O-Nitroso-4-methyl-1-(3-benzoyl-α-methylbenzeneacetic acid) pentyl ester

A solution of the product of example 5a (0.4 g, 1.13 mmol) and pyridine (456 mL, 5.6 mmol) in methylene chloride (4 mL) was cooled to -78°C and nitrosonium tetrafluoroborate (262 mg,2.26 mmol) added. The reaction mixture was stirred at -78°C for 3 hours, washed with water and dried over sodium sulfate. After filtration and evaporation of the solvent the residual oil was subjected to column chromatography using ethyl acetate/hexane/triethylamine (18:80:2). . The title compound was isolated as an oil

in 58% yield (0.25 g). ^{1}H NMR ($CDCl_3$) δ: 7.41-7.80 (m. 9 H). 4.02-4.17 (m. 2 H). 3.79 (q, J=7.2 Hz, 1 H). 1.73-1.79 (m. 2 H), 1.62-1.69 (m. 2 H). 1.52-1.55 (m. 9H).

Example 6

3-S-Nitroso-3-methyl-1-(3-benzoyl-α-methylbenzeneacetic acid) butyl ester

6a. 3-Mercapto-3-methyl-1-(3-benzoyl-α-methylbenzeneacetic acid) butyl ester

To 3-Benzoyl-α-methylbenzeneacetic acid (529 mg, 2 mmol) in benzene (5 mL) containing 5 ml of DMF was added oxalyl chloride (200 ml 2.2 mmol) dropwise. The reaction mixture was stirred 1.5 hour and then concentrated in vacuo to a syrup. The crude acid chloride was dissolved in dichloromethane (10 mL) and 3-mercapto-3-methyl butanol (Sweetman *et al. J. Med. Chem., 14*:868 (1971) (350 mg, 2.2 mmol) was added followed by pyridine (180 ml, 2.2 mmol). The reaction was stirred at room temperature for 1 hour and then it was diluted with dichloromethane and wash with 1N HCl, followed by saturated sodium bicarbonate, and then brine. The organic phase was dried over sodium sulfate, concentrated in vacuo, and the residue was chromatographed on silica gel eluting eith 9:1 hexane:ethyl acetate to afford 640 mg (90 %) of the product. ^{1}H NMR ($CDCl_3$) δ: 7.41-7.81 (m, 9 H), 4.28 (t, J = 7.1 Hz, 2 H), 3.78 (q, J = 7.2 Hz, 1 H), 1.88 (t, J = 7.0 Hz, 2 H), 1.69 (s, 1 H), 1.54 (d, J = 7.3 Hz, 3 H), 1.35 (s, 3 H), 1.34 (s, 3H).

6b. 3-S-Nitroso-3-methyl-1-(3-benzoyl-α-methylbenzeneacetic acid) butyl ester

To a solution of the product of Example 6a (105 mg, 0.3 mmol) in dichloromethane (4 mL) was added tert-butyl nitrite (70 mg, 0.6 mmol) in a dropwise fashion. The mixture was stirred at room temperature for 30 minutes. The solvent and excess reagent were evaporated to give 113 mg (quantitative) of the title compound. ^{1}H NMR ($CDCl_3$) δ: 7.44-7.81 (m, 9 H), 4.29 (t, J = 6.9 Hz, 2 H), 3.77 (q, j = 7.2 Hz, 1 H), 2.51 (t, j = 6.9 Hz, 2 H), 1.841 (s, 3 H), 1.836 (s, 3 H), 1.53 (d, J = 7.2 3H).

Example 7

4-O-Nitr so-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) butyl ester

7a. (S)-6-methoxy-α-methyl-2-naphthaleneacetic acetyl chloride

Under a nitrogen atmosphere, oxalyl chloride (4.13 g, 30 mmol) was combined with methylene chloride (30 mL) and the resulting mixture was cooled to 0°C. Dimethylformamide (10 drops) was added and after 5 minutes of stirring, a suspension of (S)-6-methoxy-a-methyl-2-naphthaleneacetic acid (3.00 g, 13 mmol) in methylene chloride (30 mL) was added dropwise over a 30 minute period. The reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent was evaporated in vacuo to give the product in a quantitative yield. ^{1}H NMR ($CDCl_3$) δ: 1.5 (d, 3 H), 3.91 (s, 1 H), 4.21 (q, 1 H), 7.09-7.14 (m, 1 H), 7.15 (d, 1 H), 7.42 (dd, 1 H), 7.68 (s, 2 H), 7.71 (s, 1H).

7b. 4-Hydroxy-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) butyl ester

Under a nitrogen atmosphere, 1,4-butanediol (5.30 mL, 60 mmol) and pyridine (0.95g, 12 mmol) were combined in methylene chloride (20 mL). The resulting solution was stirred for 5 minutes and then cooled to 0°C. A solution of the product of Example 7a (3.0 g, 12 mmol) in methylene chloride (15 ml) was added dropwise over 30 minute period. After stirring for 20 hours at room temperature, the reaction mixture was diluted with ethyl acetate and washed with 1N hydrochloric acid. The organic phase was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using hexane/ethyl acetate (1:1 to 1:3) to afford 3.09 g (79% yield) of the product as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 1.47-1.68 (m, 4H, overlapping with a doublet at 1.57, 3 H), 3.55 (t, 2 H), 3.84 (q, 1 H), 3.91 (s, 3 H), 4.11 (t, 2 H), 7.11 (m, 2 H), 7.15 (d, 1 H), 7.42 (dd, 1 H), 7.67 (s, 1 H), 7.70 (d, 2 H).

7c. 4-O-Nitroso-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) butyl ester

The product of Example 7b (0.209 g. 0.69 mmol) was dissolved in anhydrous methylene chloride (4 mL) and pyridine (0.273 g, 3.45 mmol) was added. The resulting solution was cooled to -78°C and nitrosonium tetrafluoroborate (0.161 g. 1.38 mmol) was added in one portion. The reaction mixture was stirred for 1 hour at -78°C. The solvent was evaporated in vacuo and the residue was purified by flash chromatography on silica gel , deactivated with triethylamine, eluted with ethyl acetate/hexane (1:2) to give 0.180 g (79% yield) of the title compound as an oil. ^{1}H NMR ($CDCl_3$) δ: 1.58 (d, 3 H), 1.64-1.69 (m. 4 H), 3.85 (q, 1 H), 3.92 (s, 3 H), 4.11 (t, 2 H), 4.60 (s, 2 H), 7.10-7.13 (m, 1 H), 7.15 (d, 1 H), 7.39 (dd, 1 H), 7.66 (s, 1 H), 7.70 (d, 2 H).

Example 8

4-O-Nitroso-1-(1-)4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid) butyl ester

8a. 4-Hydroxy-1-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid) butyl ester

A stirred suspension of 1(4-chlorobenzoyl)5-methoxy-2-methylindoyl)-3-acetic acid (3.7 g, 10.5 mmol) in methylene chloride (20 mL) under nitrogen and cooled over ice was treated successively with oxalyl chloride (1.8 mL, 20.6 mmol) and dimethylformamide (10 drops). A vigorous gas evolution was noted and the reaction mixture was stirred with gradual warming to room temperature and then at ambient for a total of 5 hours. The volatile materials were evaporated and the residue dissolved in dichloromethane (10 mL) and added dropwise to a precooled mixture 1,4-butanediol (4.7 g, 51.7 mmol) and pyridine (0.92 mL, 11.4 mmol) also in methylene chloride (10 mL). The reaction mixture was stirred with slow warming and then for 5 hours at ambient temperature under a nitrogen atmosphere. The solution was washed with 2N hydrochloric acid, saturated sodium bicarbonate, dried over anhydrous sodium sulfate,

filtered and concentrated *in vacuo*. The residual oil was subjected to column chromatography using ethyl acetate/hexane (1:2). The product was isolated as an oil in 75% yield (3.3 g) which solidified on standing ^{1}H NMR ($CDCl_3$) δ: 7.67 (d. J=8.4 Hz. 2 H), 7.47 (d, J=8.5 Hz. 2 H), 6.97 (d, J=2.5 Hz, 1 H), 6.87 (d, J=9 Hz. 1 H), 6.67 (dd, J=2.5 Hz, 9Hz, 1 H), 4.13 (t, J=6.4 Hz. 2 H), 3.83 (s, 3 H), 3.66 (s. 2 H). 3.59 (t, J=6.4 Hz, 2 H), 2.38 (s, 3 H), 1.51-1.75 (m. 4H). Anal calcd for $C_{23}H_{24}ClNO_5$: C, 64.26; H, 5.63; N, 3.26. Found: C, 64.08; H, 5.60; N, 3.18.

8b. 4-O-Nitroso-1-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl- 1H-indole-3-acetic acid) butyl ester

A stirred solution of the product of Example 8a (1 g, 2.3 mmol), and pyridine (0.90 mL, 11.6 mmol) in methylene chloride (15 mL) at -78 ûC under a nitrogen atmosphere was treated with nitrosonium tetrafluoroborate (0.54 g, 4.6 mmol). The reaction mixture was stirred at -78 ûC for 3.5 hours, washed with water, dried with anhydrous sodium sulfate and the solvent removed *in vacuo*. The residual oil was subjected to column chromatography using ethyl acetate/hexane (1:3). The product was isolated as a yellow oil in 69 % yield (0.73 g). ^{1}H NMR ($CDCl_3$) δ: 7.66 (d, J=8.5 Hz, 2Hz), 7.47 (d. J=8.5 Hz, 2 H), 6.95 (d, J=2.5 Hz, 1 H), 6.85 (d, J=5 Hz, 1 H), 6.66 (dd, J=2.5 Hz, 6.5 Hz, 1 H), 4.66 (br s. 2 H), 4.16 (t, J=6.6 Hz, 2 H), 3.83 (s, 3 H), 3.66 (s, 2 H), 2.39 (s, 3 H), 1.65-1.80 (m, 4H). Anal calcd for $C_{23}H_{23}ClN_2O_6$: C, 60.2; H, 5.05; N, 6.1. Found: C, 59.93; H, 4.87; N, 5.85.

Example 9

3-O-Nitroso-1-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid) butyl ester

9a. 3-Hydroxy-1-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid) butyl ester

A stirred suspension of 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid (5 g, 13.9 mmol) in methylene chloride (25 mL) under nitrogen and cooled over ice was treated successively with oxalyl chloride (2.44 mL, 28 mmol) and dimethylformamide (10 drops). A vigorous gas evolution was noted and the reaction mixture was stirred with gradual warming for a total of 5 hours. The volatile materials were removed *in vacuo* and the residue dissolved in methylene chloride (15 mL) and added dropwise to a precooled mixture (+/-)-1,3-butanediol (8.83 g, 98 mmol) and pyridine (1.24 mL, 15.4 mmol) also in dichloromethane (10 mL). The reaction mixture was stirred with slow warming and then over the weekend at ambient temperature under a nitrogen atmosphere. The solution was washed with 2N hydrochloric acid, saturated sodium bicarbonate, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual oil was subjected to column chromatography using ethyl acetate/hexane (1:1). The product was isolated as an oil which solidified on standing in 75% yield (4.5 g). ^{1}H NMR indicated that the desired product was contaminated with an isomer and so it was recrystalised three times from diethyl ether/hexanes to give the desired product as a solid in 15 % yield (0.9 g). ^{1}H NMR ($CDCl_3$) δ: 7.66 (d, J=8.5 Hz, 2 H), 7.43 (d, J=8.5 Hz, 2 H), 6.95 (d, J=2.4 Hz, 1 H), 6.86 (d, J=9 Hz, 1 H), 6.67 (dd, J=9 Hz, 2.5 Hz), 4.30-4.39 (m, 1 H), 4.15-4.4 (m, 1 H), 3.83 (s, 3 H), 3.75-3.85 (m, 1 H), 3.67 (s, 2 H), 2.38 (s, 3 H), 1.95 (s, 1 H), 1.65-2.8 (m, 2 H), 1.16 (d, J=6.3 Hz, 3H). Anal calcd for $C_{23}H_{24}ClNO_5$: C, 64.26; H, 5.63; N, 3.26. Found: C, 64.29; H, 5.53; N, 3.18.

9b. <u>3-O-Nitroso-1-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid) butyl ester</u>

A stirred solution of the product of Example 9a (0.15 g, 0.34 mmol), and pyridine (0.14 mL, 1.7 mmol) in dichloromethane (2 mL) at -78°C under a nitrogen atmosphere was treated with nitrosonium tetrafluoroborate (0.08 g, 0.7 mmol). The reaction mixture was stirred at -78°C for 3.5 hours, washed with water, dried with anhydrous sodium sulfate and the solvent removed *in vacuo*. The residual oil was subjected to column

chromatography using ethyl acetate/hexane (1:3). The title compound was isolated as a yellow oil in 79 % yield (0.125 g). ^{1}H NMR ($CDCl_3$) δ:. 7.66 (d. J=8.5 Hz. 2 H). 7.47 (d, J=8.5 Hz), 6.95 (d. J=2.3 Hz. 1 H), 6.86 (d. J=9 Hz. 1 H). 6.67 (dd, J=9 Hz. 2.5 Hz), 5.52 (sextet, J=6.5 Hz. 1 H), 4.06-4.24 (m, 2 H), 3.83 (s. 3 H). 3.65 (s. 2 H). 2.38 (s, 3 H), 2.05 (q, J=4 Hz, 2 H), 1.37 (d, J=6.5 Hz).

Example 10

4-O-Nitroso-4 methyl-1-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid) pentyl ester

10a. 4-Hydroxy-4 methyl-1-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid) pentyl ester

A stirred suspension of 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid (2.8 g, 7.7 mmol) in methylene chloride (25 mL) under nitrogen and cooled over ice was treated successively with oxalyl chloride (1.36 mL, 15.7 mmol) and dimethylformamide (5 drops). A vigorous gas evolution was noted and the reaction mixture was stirred over ice for 30 minutes and then at room temperature for 3 hours. The volatile materials were removed *in vacuo* and the residue dissolved in methylene chloride (15 mL) and added dropwise to a precooled mixture of 2-methyl-2,5-pentanediol (3.7 g, 31 mmol) and pyridine (0.69 mL, 8.6 mmol) also in methylene chloride (10 mL). The reaction mixture was stirred under nitrogen with slow warming and then overnight at ambient temperature under a nitrogen atmosphere. The solution was washed with 2N hydrochloric acid, dried over anhydrous sodium sulfate, and filtered to give an oil which was concentrated *in vacuo*. The residual oil was subjected to column chromatography using ethyl acetate/hexane (1:2) The product was isolated as an oil which solidified on standing in 100% yield (3.6 g). ^{1}H NMR ($CDCl_3$) δ: 7.69 (d. J=8.9 Hz, 2 H), 7.47 (d, J=8.9 Hz, 2 H), 6.98 (d, J=2.5 Hz, 1 H), 6.87 (d. J=9 Hz, 1 H), 6.67 (dd, J=9 Hz, 2.5 Hz), 4.09-4.14 (m, 2 H), 3.83 (s, 3 H), 3.66 (s, 3 H), 2.39 (s, 3 H), 1.62-1.73 (m, 2

H), 1.37-1.43 (m. 2 H), 1.14 (s. 6H). Anal calcd for $C_{25}H_{28}ClNO_5$: C. 65.57: H. 6.16: N, 3.06. Found: C, 65.35; H. 6.25; N, 3.10.

10b. 4-O-Nitroso-4-methyl-1-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid) pentyl ester

A solution the product of Example 10a (0.2 g, 0.44 mmol) and pyridine (176 mL. 2.2 mmol) in methylene chloride (2 mL) was cooled over dry ice and nitrosonium tetrafluoroborate (101 mg, 0.87 mmol) added. The reaction mixture was stirred at -78 ¡C for 3 hours, allowed to stand at the same temperature overnight, washed with water and dried over sodium sulfate. After filtration and evaporation of the solvent the residual oil was subjected to column chromatography (twice) using ethyl acetate/hexanes/triethylamine (25:73:2). The product was isolated as an oil in 42% yield (0.09 g). ^{1}H NMR ($CDCl_3$) δ: 7.66 (d, J=7.5 Hz, 2 H), 7.47 (d, J=7.5 Hz, 2 H). 6.96 (d, J=2.5 Hz, 1 H), 6.86 (d, J=9 Hz, 1 H), 6.66 (dd, J=7.5 Hz, 2.5 Hz), 4.11 (t, J=6Hz. 2 H), 3.83 (s, 3 H), 3.66 (s, 2 H), 2.39 (s, 3 H), 1.75-1.81 (m, 2 H), 1.64-1.72 (m, 2 H), 1.51 (s, 6H).

Example 11

3-S-Nitroso-3-methyl-1-(α-methyl-4-(2-methylpropyl)benzeneacetic acid) butyl ester

11a. 3-Mercapto-3-methyl-1-(α-methyl-4-(2-methylpropyl)benzeneacetic acid) butyl ester

A solution of α-methyl-4-(2-methylpropyl)benzeneacetic acid (1.52 g, 7.4 mmol) in methylene chloride (15 mL) cooled over ice and under nitrogen, was treated successively with oxalyl chloride (1.29 mL, 1.88 g, 14.8 mmol) and dimethylformamide (5 drops). The resultant solution was stirred over ice for 30 minutes and then at ambient temperature for 2 hours. The excess volatile materials were removed *in vacuo*

and the residue, dissolved in methylene chloride (5 mL), added to a precooled solution of pyridine (0.54 mL, 6.7 mmol) and 3-mercapto-3-methylbutanol (0.8 g, 6.7 mmol) in methylene chloride (15 mL). The reaction mixture was stirred over ice for 30 minutes and then at ambient temperature for 3 hours. The solution was then diluted with additional methylene chloride and washed with 2N hydrochloric acid, saturated sodium bicarbonate and brine and the organic phase dried with sodium sulfate, filtered and the solvent removed *in vacuo*. The residual oil was subjected to column chromatography using ethyl acetate/hexane (1:3). The product was isolated as an oil in 68 % yield (1.4 g). ^{1}H NMR ($CDCl_3$) δ: 7.18 (d, J=7.5 Hz, 2 H), 7.09 (d, J=7.5 Hz, 2 H), 4.25 (t, J=6.5 Hz, 2 H), 3.67 (q, J=7 Hz, 1 H), 2.44 (d, J=7.8 Hz, 2 H), 1.77-1.9 (m, 3 H), 1.48 (d, J=7 Hz, 3 H), 1.32 (s, 6 H), 0.89 (d, J=6.6 Hz, 6H).

11b. 3-S-Nitroso-3-methyl-1-(α-methyl-4-(2-methylpropyl)benzeneacetic acid) butyl ester

A solution of the product of Example 11a (0.4 g, 1.2 mmol) in methylene chloride (8 mL) under nitrogen was treated with *tert* butyl nitrite (0.62 mL, 0.53 g, 5 mmol). After stirring for 1 hour at ambient temperature the volatile materials were evaporated. The residual green oil was subjected to column chromatography using ethyl acetate/hexanes (1:19). The product was isolated as a green oil in 65 % yield (0.25 g). ^{1}H NMR ($CDCl_3$) δ: 7.0 (d, J=7.5 Hz, 2 H), 7.10 (d, J=7.5 Hz, 2 H), 4.27 (t, J=6.9 Hz, 2 H), 3.66 (q, J=7.2 Hz, 1 H), 2.49 (t, J=6.6 Hz, 2 H), 2.44 (d, J=7.2 Hz, 2 H), 1.8-1.9 (m, 1 H), 1.81 (s, 3 H), 1.80 (s, 3 H), 1.48 (d, J=7.2 Hz, 3 H), 0.89 (d, J=6.6 Hz, 6H).

Example 12

4-O-Nitroso-1-(α-methyl-4-(2-methylpropyl)benzeneacetic acid) butyl ester

12a. 4-Hyroxy-1-(α-methyl-4-(2-methylpropyl)benzeneacetic acid) butyl ester

α-Methyl-4-(2-methylpropyl)benzeneacetic acid (4 g. 19 mmol) and 10 μL DMF were dissolved in benzene (30 mL). Oxalyl chloride was added dropwise. Stirring was continued for 2 hour before concentration to a syrup. Butanediol (9 mL, 100 mmol) and pyridine (1.67 mL, 21 mmol) were dissolved in dichloromethane (100 mL) and dioxane (15 mL) and cooled to 0°C. A solution of the acid chloride was added in dichloromethane (20 mL). The reaction mixture was stirred cold for 20 minutes then warmed to room temperature with stirring for 2 hour. The solution was washed H_2O, 1 N HCl, satd sodium bicarbonate and finally brine; dried over sodium sulfate: and evaporated. The residue was filtered through silica gel eluting with 2:1 hexane:EtOAc to yield 4.8 g (91 %) ofthe product. ^1H NMR ($CDCl_3$) δ: 7.19 (d, J = 6.2 Hz, 2 H). 7.08 (d, J = 8.2 Hz, 2H),4.07-4.12 (m, 2 H), 3.68 (q, J = 7.1 Hz, 1 H), 3.58 (t, J = 6.3 Hz, 1 H), 2.44 (d, J = 7.2 Hz, 2 H), 1.84 (sept, J = 6.8 Hz, 1 H), 1.50-1.69 (m, 4 H), 1.48 (d, J = 7.2 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 6H). Anal Calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.17; H. 9.67

12b. 4-O-Nitroso-1-(α-methyl-4-(2-methylpropyl)benzeneacetic acid) butyl ester

The product of Example 12a (1 g, 3.6 mmol) and pyridine (1.4 mL, 18 mmol) were dissolved in dichloromethane (15 mL) and cooled to -78°C. Nitrosonium tetrafluoroborate(840 mg, 7.2 mmol) was added and the solution was kept cold for 30 minutes. The reaction was warmed to room temperature with continued stirring for 1 hour. The mixture was diluted with dichloromethane and washed successively with 1N HCl, H_2O, and brine. The solution was dried over sodium sulfate and evaporated. Chromatography on silica gel eluting with 9:1 hexane:EtOAc gave 840 mg (76 %) of the title compound. ^1H NMR ($CDCl_3$) δ: 7.18 (d, J = 8.1 Hz, 2 H), 7.08 (d, J = 8.1 Hz, 2 H). 4.62 (m, 2 H), 4.07-4.12 (m, 2 H), 3.68 (q, J = 7.1 Hz, 1 H), 2.44 (d, J = 7.2 Hz, 2 H), 1.84 (sept, J = 6.7 Hz, 1 H), 1.64-1.68 (m, 4 H), 1.48 (d, J = 7.2 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 6H).

Example 13

4-O-Nitroso-1-(2-Fluoro-α-methyl-biphenylacetic acid) butyl ester

13a. 2-Fluoro-α-methyl-biphenylacetic acid chloride

Under a nitrogen atmosphere, oxalyl chloride (3.8 g, 30 mmol) was combined with methylene chloride (30 mL). The resulting mixture was cooled to 0°C and dimethylformamide (10 drops) was added. After 5 minutes of stirring a solution of 2-fluoro-α-methyl-biphenylacetic acid (3.0 g, 12 mmol) in methylene chloride (30 mL) was added dropwise over a 30 minute period. The reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent was evaporated to give the product in a quantitative yield as a yellow solid. ^{1}H NMR ($CDCl_3$) δ:1.58 (d, 3 H), 4.20 (q, 1 H), 7.11 (t, 2 H), 7.33-7.47 (m,Ê4 H), 7.54 (d, 2 H).

13b. 4-Hydroxy-1-(2-Fluoro-α-methyl-biphenylacetic acid) butyl ester

Under a nitrogen atmosphere, 1,4-butanediol (5.30 mL, 60 mmol) and pyridine (0.95Êg,Ê12 mmol) were combined in methylene chloride (20 mL). The resulting solution was stirred for 5 minutes and then cooled to 0°C. A solution of the product of Example 13a (3.0 g, 12 mmol) in methylene chloride (15 ml) was added dropwise over 30 minute period. After stirring for 20 hours at room temperature, the reaction mixture was diluted with ethyl acetate and washed with 1N hydrochloric acid. The organic phase was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography on silica-gel eluting with methylene chloride/hexane (2:1) to give 1.66 g (44 %) of the product as a colorless oil. ^{1}H NMR ($CDCl_3$) δ:1.56 (d, 3 H), 1.61-1.77 (m, 4 H), 3.63 (t, 2 H), 3.75 (q,1 H), 4.14 (t, 2 H), 7.14 (t, 2 H), 7.27-7.45 (m, 4 H), 7.53 (d, 2 H).

13c. 4-O-Nitroso-1-(2-Fluoro-α-methyl-biphenylacetic acid) butyl ester

The product of Example 13b (0.190 g, 0.60 mmol) was dissolved in anhydrous methylene chloride (4 mL) and pyridine (0.237 g, 3.00 mmol) was added. The resulting solution was cooled to -78 ¡C and nitrosonium tetrafluoroborate (0.084 g, 0.72 mmol) was added. The reaction mixture was stirred for 1 hour at -78 ¡C and an additional nitrosonium tetrafluoroborate (0.047 g, 0.40 mmol) was added. After 30 minutes of stirring at -78 ¡C, the solvent was evaporated in vacuo and the residue was purified by flash chromatography on silica gel , deactivated with triethylamine, eluted with methylene chloride/hexane (3:1) to give 0.117 g (57 % yield) of the title compound. ^{1}H NMR ($CDCl_3$) δ: 1.54 (d, 3 H), 1.68-1.83 (m, 4 H), 3.75 (q, 1 H), 4.14 (t, 2 H), 4.67 (s, 2 H), 7.14 (t, 2 H), 7.34-7.48 (m, 4 H), 7.54 (d, 2 H).

Example 14

4-O-Nitroso-1-(2-Fluoro-α-methyl-biphenylacetic acid) thiobutyl ester

14a. 1-tert-Butyldimethylsilyloxy-4-chloro-butanol

4-Chloro-1-butanol (5.43 g, 50 mmol) was dissolved in dimethylformamide (50ÊmL) and tert-butyldimethylsilylchloride (7.54 g, 50 mmol) was added, followed by imidazole (3.4 g, 50 mmol). After 24 hours of stirring at room temperature, the reaction mixture was diluted with hexane, washed with water and brine and dried over anhydrous sodium sulfate. The solvent was evaporated to give colorless liquid which was purified by chromatography on silica gel eluting with hexane/ethyl acetate (30:1) to give the product (7.26 g, 56 %). ^{1}H NMR ($CDCl_3$) δ: 0.05 (s, 6 H), 0.89 (s, 9 H), 1.64-1.68 (m, 2 H), 1.82-1.86 (m, 2 H), 3.57 (t, 2 H), 3.64 (t, 2 H).

14b. 4-tert-Butyldimethylsilyloxy-1-acetyl-thio-butyl ester

Under a nitrogen atmosphere, potassium thioacetate (0.53 g, 4.7 mmol) was dissolved in dimethylformamide (12 mL) and cooled to 0°C. A solution of the product of Example 14a (1.01 g, 3.91 mmol) in dimethylformamide (14 mL) was added. After 24 hours of stirring at room temperature, the solvent was evaporated and the residue was partioned between hexane and water (1:3). The organic layer was concentrated in vacuo to give the product (0.820 g, 71 %) as a yellow liquid. ^{1}H NMR ($CDCl_3$) δ: 0.04 (s, 6 H), 0.88 (s, 9 H), 1.57-1.64 (m, 4 H), 2.32 (s, 3 H), 2.89 (t, 2 H), 3.61 (t, 2 H).

14c. 4-tert-Butyldimethylsilyloxy-1-butane thiol

The product of Example 14b (5.7 g, 19.2 mmol) was dissolved in methanol (30 mL) and degassed with nitrogen gas for 30 minutes. Potassium carbonate (2.92 g, 21.1 mmol) was added in one portion at room temperature. After 1 hour of stirring at room temperature, the solvent was evaporated and the residue was partioned between hexane and water. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give the product (3.2 g, 66 %). ^{1}H NMR ($CDCl_3$) δ: 0.05 (s, 6 H), 0.89 (s, 9 H), 1 34 (t, 1 H), 1.61-1.68 (m, 4 H), 2.51-2.57 (q, 2 H), 3.62 (t, 2 H).

14d. 4-tert-Butyldimethylsilyloxy-1-(2-Fluoro-α-methyl-biphenylacetic acid) thio-butyl ester

The product of Example 14c (1.37g, 5.4 mmol) was combined with pyridine (0.142Êg, 1.8 mmol) in methylene chloride (5 mL) and the resulting solution was cooled to 0 ¡C. A solution of the product of Example 13a (0.500 g, 1.8 mmol) in methylene chloride (4 mL) was added dropwise. After 22 hours of stirring at room temperature, the reaction mixture was diluted with ethyl acetate and washed with 1N hydrochloric acid. The organic layer was dried over anhydrous sodium sulfate and concentrated in

vacuo to give the product (0.526 g, 59 %). ^{1}H NMR ($CDCl_3$) δ: 0.04 (s, 6 H). 0.89 (s, 9ÊH),1.56 (d, 3 H), 1.57-1.62 (m, 4 H), 1.88-2.29 (M, 2 H). 3.61 (t, 2 H). 7.15 (t,Ê2 H), 7.37-7.44 (m, 4 H), 7.54 (d, 2 H).

14e. 4-Hydroxy-1-(2-Fluoro-α-methyl-biphenylacetic acid) thio-butyl ester

The product of Example 14d (0.320 g, 0.64 mmol) was dissolved in the mixture of glacial acetic acid (0.5 mL), water (1 mL), and tetrahydrofuran (5 mL). The resulting solution was stirred for 24 hours at room temperature. The solvent was evaporated and the residue was partioned between methylene chloride and water. The organic layer was washed with saturated sodium bicarbonate solution and brine, and dried over anhydrous sodium sulfate. The solvent was evaporated to give the product (0.235 g, 100 %). ^{1}H NMR ($CDCl_3$) δ: 1.57 (d, 3 H), 1.58-1.69 (m, 4 H), 2.87 -2.93 (m, 2 H), 3.63 (t, 2 H), 3.84-3.92 (q, 1 H), 7.14 (t, 2 H), 7.37-7.44 (m, 4 H), 7.54 (d, 2 H).

14f. 4-O-Nitroso-1-(2-Fluoro-α-methyl-biphenylacetic acid) thio-butyl ester

The product of Example 14e (0.235 g, 0.61 mmol) was dissolved in anhydrous methylene chloride (3 mL) and pyridine (0.097 g, 1.23 mmol) was added. The resulting solution was cooled to -78°C and nitrosonium tetrafluoroborate (0.144 g, 1.23 mmol) was added in one portion. The reaction mixture was stirred for 1 hour at -78°C, the solvent was evaporated, and the residue was purified by chromatography on silica gel eluted with hexane/ethyl acetate (10:1) to give the title compound (0.110 g, 44 %). ^{1}H NMR ($CDCl_3$) δ: 157 (d, 3 H), 1.58-1.80 (m, 4 H), 3.85-3.93 (q, 1 H), 4.69 (t, 2 H), 7.14 (t, 2 H), 7.37-7.44 (m, 4 H), 7 55 (d, 2 H).

Example 15

4-O_Nitroso-2-methyl-N-2-pyridinyl-2-H-1,2-benzothiazine-2-carboxamide-1,1-dioxide

4-Hydroxy-2-methyl-N-2-pyridinyl-2-H-1,2-benzothiazine-2-carboxamide-1,1-dioxide (10.0 g, 30 mmol) was dissolved in anhydrous methylene chloride and cooled to 0 ¡C. Nitrosonium tetrafluoroborate (4.407 g, 38 mmol) was added in one portion, followed by pyridine (2.98 g, 38 mmol). The reaction mixture was stirred at room temperature for 7 days and then additional nitrosonium tetrafluoroborate (0.571 g, 1.72 mmol) was added. After stirring for 14 days at room temperature, the reaction mixture was poured into saturated sodium bicarbonate solution and extracted with methylene chloride. The solvent was evaporated, the residue was treated with ethyl acetate and filtered. The precipitate was dissolved in the mixture of methylene chloride/ ethyl acetate (1:1), and the solution was treated with decolorizing charcoal, filtered and concentrated in vacuo to give the title compound as a solid (1.56 g, 14 %). ^{1}HÊNMR ($CDCl_3$, 300 MHz), δ_2.96 (s, 3 H), 6.84 (t, 1 H), 7.17 (t, 1 H), 7.60-7.86 (m, 5 H), 8.22 (d, 1 H).

Example 16

4-O-Nitroso-hydroxymethylene-(1-(3-benzoyl-α-methylbenzeneacetic acid)) benzyl ester

16a. 3-benzoyl-α-methylbenzeneacetic acid chloride

3-Benzoyl-α-methylbenzeneacetic acid (3.2 g, 12.6 mmol) was treated in the same manner as set forth in Example 13a. Evaporation of the solvent, affored the the product as a yellow oil in a quantitative yield. ^{1}H NMR ($CDCl_3$), δ1.64 (d, 3 H), 4.21 (q, 1 H), 7.45-7.51 (m, 4 H), 7.62 (d, 1 H), 7 72-7.82 (m, 4 H).

16b. 4-Hydroxymethylene-(1-(3-benzoyl-α-methylbenzeneacetic acid)) benzyl ester

Under a nitrogen atmosphere, 1,4-benzenedimethanol (0.507 g, 3.67 mmol) and pyridine (0.145 g, 1.83 mmol) were combined in methylene chloride (5 mL). The resulting solution was stirred for 5 minutes and then cooled to 0°C. A solution of the product of Example 16a (0.500 g, 1.83 mmol) in methylene chloride (5 mL) was added dropwise over 15 minutes. The reaction mixture was allowed to warm to room temperature and was then stirred over 2 days period. The solvent was evaporated and the residue was dissolved in ethyl acetate, washed with 1N hydrochloric acid and saturated sodium bicarbonate solution. The organic phase was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography on silica-gel eluting with hexane/ethyl acetate (5:1 to 2:1) to give 0.092 g (42 %) of the product. ^{1}H NMR ($CDCl_3$) δ:1.60 (d, 3 H), 2.19 (s, 1 H), 3.90 (q, 1 H), 4.71 (s, 2 H), 5.17 (s, 2 H), 7.32 (dd, 4 H), 7 45-7.82 (m, 7 H), 7 84 (d, 2 H).

16c. 4-O-Nitroso-hydroxymethylene-(1-(3-benzoyl-α-methylbenzeneacetic acid)) benzyl ester

The product of Example 16b (0.090 g, 0.24 mmol) was treated in the same manner as set forth in Example 7c. Purification of the crude product was accomplished using flash chromatography on silica gel eluted with hexane/ethyl acetate (1:2) to give 0.069 g (71 %) of the title compound as a yellow oil. ^{1}H NMR ($CDCl_3$, 300ÊMHz). δ1.55 (d, 3 H), 3.85 (q, 1 H), 5.11 (s, 2 H), 5.67 (s, 2 H), 7.27-7.80 (m, 9 H).

Example 17

3-O-Nitroso-hydroxymethylene-(1-(3-benzoyl-α-methylbenzeneacetic acid)) benzyl ester

17a. 3-Hydroxymethylene-(1-(3-benzoyl-α-methylbenzeneacetic acid)) benzyl ester

Under a nitrogen atmosphere, 1,3-benzenedimethanol (0.500 g, 3.62 mmol) and pyridine (0.193 g, 2.44 mmol) were combined in methylene chloride (7 mL). The resulting solution was stirred for 5 minutes and then cooled to 0°C. A solution of the the product of Example 16a (0.665 g, 2.44 mmol) in methylene chloride (5 mL) was added dropwise over 15 minutes. The reaction mixture was stirred 2 hour 30 minutes at 0°C, concentrated in vacuo, diluted with ethyl acetate, washed with 1N hydrochloric acid and saturated sodium bicarbonate solution. The organic phase was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with hexane/ethyl acetate (2:1) to give 0.530 g (58 %) of the product. ^{1}H NMR ($CDCl_3$) δ:1.55 (d, 3 H), 3.85 (q, 1 H), 4.64 (s, 2 H), 5.12 (d, 2 H), 7.13-7.18 (m, 1 H), 7.22 (s, 1 H), 7.26-7.30 (m, 2 H), 7.40-7.67 (m, 6 H), 7 73-7.78 (m, 3 H).

17b. 3-O-Nitroso-hydroxymethylene-(1-(3-benzoyl-α-methylbenzeneacetic acid)) benzyl ester

The product of Example 17a (0.74 g, 0.198 mmol) was treated in the same manner as set forth in Example 7c. Purification of the crude product was accomplished using flash chromatography on silica gel eluted with hexane/ethyl acetate (2:1) to give 0.046 g (71 %) of the title compound. ^{1}HÊNMR ($CDCl_3$) δ:1.55 (d, 3 H), 3.85 (q, 1 H), 5.12 (s, 2 H), 5.65 (s, 2 H), 7.18-7.31 (m, 4 H), 7.40-7.75 (m, 6 H), 7.76-7.79 (m, 3 H).

Example 18

3-O-Nitroso-hydroxymethylene-1-(1-(3-benzoyl-α-methylbenzeneacetic acid))-hydroxymethyladamantyl ester

18a. 1,3-Dicarboxymethyl adamantane

1,3-adamantanedicarboxylic acid (1.5 g, 5.95 mmol) was dissolved in methanol (30mL) and concentrated sulfuric acid (0.5 mL, 8.90 mmol) was added. The reaction

mixture was stirred at room temperature 20 hours. After concentration in vacuo, the residue was dissolved in methylene chloride, washed with water/brine (1:1), and dried over anhydrous sodium sulfate. The solvent was evaporated to give the product as a white solid in a quantitative yield. ^{1}H NMR ($CDCl_3$) δ:1.65-1.71 (m, 2 H), 1.76-1.82 (m, 8 H), 1.98-2.03 (m, 2ÊH), 2.07-2.18 (m, 2 H), 3.66 (s, 6 H).

18b. 1,3-Dihydroxymethyl adamantane

Under a nitrogen atmosphere, the product of Example 18a (1.33 g, 5.95 mmol) was dissolved in tetrahydrofuran (20 mL) and lithium aluminum hydride (0.316 g, 8.33 mmol) was added in one portion. The reaction mixture was allowed to reflux for 30 minutes, and was then quenched with water (0.316 mL, 8.33 mmol), 15 % sodium hydroxide solution (0.316 mL), and water (0.95 mL). After 15 hours of stirring at room temperature, the reaction mixture was filtered through PTFE and filtrate was partitioned between ethyl acetate and brine. The organic phase was dried over anhydrous sodium sulfate, filtered through PTFE and concentrated in vacuo to give the product (0.370 g, 28 %) as a white solid. ^{1}H NMR ($CDCl_3$) δ:1.24-1.29 (m, 2 H), 1.42-1.52 (m, 8 H), 1.61-1.68 (m, 2 H), 2.07-2.16 (m, 2 H), 3.25 (s, 4 H).

18c. 3-Hydroxymethylene-1-(1-(3-benzoyl-α-methylbenzeneacetic acid))-hydroxymethyladamantyl ester

The product of Example 18b (0.199 g,0.54 mmol) was dissolved in tetrahydrofuran (10 mL) and pyridine (0.047 g, 0.59 mmol) was added. A solution of the product of Example 16a (0.161 g, 0.59 mmol) in chloroform (3 mL) was added dropwise. The reaction mixture was stirred at room temperature for 40 hours. The solvent was evaporated, the residue was dissolved in methylene chloride, washed with 1N hydrochloric acid, saturated sodium bicarbonate solution and brine, and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by flash chromatography on silica gel eluted with hexane/ethyl acetate (2:1) to give the

product (0.102 g, 28 %) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ:1.13-1.17 (m, 2 H), 1.18-1.55 (m, 10 H), 1.98-2.02 (m, 2 H), 3.18 (s, 2 H), 3.66 (d, 1 H), 3.77 (d, 1 H), 3.83 (q, 1 H), 7.43-7.68 (m, 6 H), 7.76-7.81 (m, 3 H).

18d. 3-O-Nitroso-hydroxymethylene-1-(1-(3-benzoyl-α-methylbenzeneacetic acid))-hydroxymethyladamantyl ester

The product of Example 18c (0.056 g, 0.083 mmol) was dissolved in anhydrous methylene chloride (2 mL) and pyridine (2 drops) was added. The resulting solution was cooled to -78°C and nitrosonium tetrafluoroborate was added in one portion. The reaction mixture was stirred for 3 hours at -78°C, washed with water, brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by chromatography on silica gel eluted with hexane/ethyl acetate (15:1) to give the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$) δ:1.15-1.19 (m, 2 H), 1.29-1.61 (m, 10 H), 1.98-2.03 (m, 2 H), 3.65 (d, 1 H), 3.77 (d, 1 H), 3.82 (q, 1 H), 4.33 (s, 2 H), 7.43-7.68 (m, 6 H), 7.76-7.81 (m, 3 H).

Example 19

3-(2-S-Nitroso-2-methyl propionic acid propyl amide)-2-amino-1-(α-methyl-4-(2-methylpropyl)benzeneacetic acid) propyl ester hydrochloride

19a. 2-Mercapto-2-methyl-1-(2-tert-butyloxycarbamoyl-3-hydroxy-propionic acid) propyl amide

2-tert-Butyloxycarbamoyl-3-hydroxy-propionic acid (5 g, 24 mmol), 1-amino-2-methyl-2-propanethiol-HCl (3.5 g, 25 mmol), triethylamine (3.4 mL, 25 mmol), and 4-dimethylaminopyridine (300 mg, 2.4 mmol) were dissolved in methylene chloride (120 mL). DCC (5.1 g, 24 mmol) was added and the reaction mixture was stirred at room temperature overnight. The precipitate which formed was removed by filtration and washed with Et_2O. The mixed solvents were allowed to stand and more solid precipitated. This was removed by filtration and the mother liquor was

evaporated to leave 7.3 g of syrup. ^{1}H-NMR (DMSO-d_6): δ 7.78 (t, J = 5.6 Hz, 1 H), 6.69 (d, J = 7.8 Hz, 1 H), 4.82 (br s, 1 H), 3.96 (mult, 1 H), 3.54 (mult, 2 H), 3.32 (mult, 1H, obscured by H2O), 2.73 (dd, J = 5.6 and 13.3 Hz, 1 H), 1.37 (s, 9 H), 1.22 (s, 3 H), 1.20 (s, 3H). Anal calcd for $C_{12}H_{24}N_2O_4S$: C, 49.29; H, 8.27; N, 9.58; S, 10.96. Found: C, 49.39; H, 8.01; N, 9.44; S, 10.96.

19b. 3-(2-Mercapto-2-methyl propionic acid propyl amide)-2-tert-butyloxycarbamoyl-1-(α-methyl-4-(2-methylpropyl)benzeneacetic acid) propyl ester

1-α-methyl-4-(2-methylpropyl)benzeneacetic acid (1.4 g, 6.8 mmol) and 10 μL of DMF were slurried in benzene (10 mL). Oxalyl chloride (630 μL, 7.2 mmol) was added dropwise. The reaction mixture was allowed to stir at room temperature for 1 hour. The volatiles were removed on a rotary evaporator and the residue was reconcentrated from 5 mL of benzene. The reisdue was taken up in methylene chloride (10 mL) and cooled to 0°C. To this solution was added the product of Example 19a (2 g, 6.8 mmol) and pyridine (570 uL, 6.8 mmol) in methylene chloride (14 mL). The reaction was kept cold for 15 minutes then allowed to warm to room temperature. After 1 hour the mixture was diluted with methylene chloride and washed (1 X 10 ml) with 0.3 N HCl and satd $NaHCO_3$. The solvent was dried over Na_2SO_4 and evoporated in vacuo to leave 3.04 g of product as a mixture of inseparable diastereomers. ^{1}H-NMR ($CDCl_3$) δ: 7.15-7.18 (mult, 2 H), 7.07-7.14 (mult, 2 H), 6.57 (mult, 1 H), 5.24 and 5.04 (br s, 1 H), 4.48 (dd, J = 4.3 and 10.6 Hz, 1 H), 4.44 (dd, J = 5.0 and 10.6 Hz, 1 H), 4.28 (dd, J = 5.0 and 11.5 Hz, 1 H), 4.25 (mult, 1 H), 3.71 (q, J = 7.2 Hz, 1 H), 3.69 (q, J = 7.2 Hz, 1 H), 3.32 (dd, J = 6.7 and 13.6 Hz, 1 H), 3.21-3.24 (mult, 1 H), 3.17 (dd, J = 5.4 and 12.7 Hz, 1 H), 2.43 and 2.41 (d, J = 7.1 Hz, 2 H), 1.84 (sept, J = 6.7 Hz, 1 H), 1.46 and 1.47 (d, J = 7.1 Hz, 3 H), 1.43 (s, 9 H), 1.30 (s, 3 H), 1.28 (s, 3 H), 0.88 (d, J = 6.6 Hz, 6H). Anal calcd for $C_{25}H_{40}N_2O_5S$: C, 62.47; H, 8.39; N, 5.83; S, 6.67. Found: C, 62.78; H, 8.30; N, 5.69; S, 6.31.

19c. 3-(2-S-Nitroso-2-methyl propionic acid propyl amide)-2-amino-1-(α-methyl-4-(2-methylpropyl)benzeneacetic acid) propyl ester hydrochloride

The product of Example 19b (630 mg, 1.3 mmol) and tert-butyl nitrite (190 uL, 1.6 mmol) were dissolved in methylene chloride (8 mL) and stirred at room temperature for 1.5 hour. The solvent was evaporated and the residue was filtered through silica gel to give 430 mg of nitrosothiol. The amine protecting group was removed by stirring in 3N HCl in EtOAc (6 mL) for 1 hour. The solvent was removed to give 360 mg (62 % overall) of nitrosothiol hydrochloride (mixture of diastereomers) as a green solid. ^{1}H-NMR ($CDCl_3$) δ : 8.94-9.00 (mult, 1 H), 8.49 (br s, 3 H), 7.04-7.18 (mult, 4 H), 4.40-4.47 (mult, 1 H), 4.13 (mult, 2 H), 3.94-4.01 (mult, 1 H), 3.71-3.77 (mult, 2 H), 2.39/2.37 (d, J = 6.0 Hz, 2 H), 1.83/1.80/1.78/1.73 (s, 6 H), 1.36 (d, J = 6.0 Hz, 3 H), 0.83 (d, J = 6.4 Hz, 6H).

Example 20

3-(2-S-Nitroso-2-methyl propionic acid propyl amide)-2-amino-1-(3-benzoyl-α-methylbenzeneacetic acid) propyl ester hydrochloride

20a. 3-(2-Mercapto-2-methyl propionic acid propyl amide)-2-tert-butyloxycarbamoyl-1-(3-benzoyl-α-methylbenzeneacetic acid) propyl ester

3-Benzoyl-α-methylbenzeneacetic acid (1.75 g, 6.8 mmol) and 10 uL of DMF were slurried in benzene (10 mL). Oxalyl chloride (630 uL, 7.2 mmol) was added dropwise. The reaction mixture was allowed to stir at room temperature for 1 hour. The volatiles were removed on a rotary evaporator and the residue was reconcentrated from 5 mL of benzene. The reisdue was taken up in methylene chloride (10 mL) and cooled to 0 °C. To this solution was added the product of Example 19a (2 g, 6.8 mmol) and pyridine (570 uL, 6.8 mmol) in methylene chloride (14 mL). The reaction was kept cold for 15 minutes then allowed to warm to room temperature. After 1 hour the mixture was diluted with methylene chloride and washed (1 X 10) with 0.3 N HCl and satd $NaHCO_3$. The solvent was dried over Na_2SO_4 and removed on a rotary evaporator to leave 3.4 g of product.

Chromatography on silica gel eluting with 2:1 Hex:EtOAc gave 1.89 g (53%) of an inseparable mixture of diastereomers. ^{1}H-NMR ($CDCl_3$) δ:7.77-7.82 (mult, 3 H), 7.55-7.67 (mult, 2 H), 7.41-7.52 (mult, 4 H), 6.72-6.77 (mult, 1 H), 5.24 and 5.01 (br s, 1 H), 4.26-4.55 (mult, 3 H), 3.83 (q, J = 7.2 Hz, 1 H), 3.14-3.78 (mult, 2 H), 1.42 and 1.41 (s, 9 H), 1.32, 1.30, and 1.28 (s, 6H). Anal calcd for $C_{28}H_{36}N_2O_6S$: C, 63.61; H, 6.86; N, 5.30; S, 6.06. Found: C, 63.80; H, 6.76; N, 5.10; S, 5.88.

20b. 3-(2-S-Nitroso-2-methyl propionic acid propyl amide)-2-amino-1-(3-benzoyl-α-methylbenzeneacetic acid) propyl ester hydrochloride

The product of Example 20a (520 mg, 1.0 mmol) and tert-butyl nitrite (140 μL, 1.2 mmol) were dissolved in methylene chloride (8 mL) and stirred at rooom temperature for 1.5 hour. The solvent was evaporated and the residue was filtered through a plug of silica gel to give 350 mg of nitrosothiol. The amine protecting group was removed by stirring in 3N HCl in EtOAc (6 mL) for 1 hour. The solvent was evaporated to give 290 mg (58 % overall) of the title compound (mixture of diastereomers) as a green solid. ^{1}H-NMR ($CDCl_3$) δ:8.94-9.01 (mult, 1 H), 8.47 (3 H), 7.48-7.73 (mult, 9 H), 4.39-4.47 (mult, 1 H), 4.16 (mult, 2 H), 3.89-4.06 (mult, 2 H), 3.69-3.77 (mult, 1 H), 1.89/1.81/1.79/1/70 (s, 6 H), 1.43/1.42 (d, J = 7.1 Hz, 3H).

Example 21

3-(2-S-Nitroso-2-methyl propionic acid propyl amide)-2-amino-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) propyl ester hydrochloride

21a. 3-(2-Mercapto-2-methyl propionic acid propyl amide)-2-tert-butyloxycarbamoyl-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) propyl ester

(S)-6-methoxy-α-methyl-2-naphthaleneacetic acid (1.75 g, 7.6 mmol) and 10 μL of DMF were slurried in benzene (10 mL). Oxalyl chloride (760 μL, 7.6 mmol) was added dropwise. The reaction mixture was allowed to stir at room temperature for 1

hour. The volatiles were evaporated on a rotary evaporator and the residue was reconcentrated from 5 mL of benzene. The reisdue was taken up in methylene chloride (10 mL) and cooled to 0°C. To this solution was added the the product of Example 19a (2.2 g, 7.6 mmol) and pyridine (630 μL, 7.6 mmol) in methylene chloride (14 mL). The reaction was kept cold for 15 minutes then allowed to warm to room temperature. After 1 hour the mixture was diluted with methylene chloride and washed (1 X 10) with 0.3 N HCl and satd $NaHCO_3$. The solvent was dried over Na_2SO_4 and evaporated on a rotary evaporator. ^{1}H-NMR ($CDCl_3$) δ: 7.72 (d, J = 8.5 Hz, 1 H), 7.70 (d, J = 8.6 Hz, 1 H), 7.64 (s, 1 H), 7.37 (dd, J = 1.8 and 8.5 Hz, 1 H), 7.15 (dd, J = 2.5 and 8.9 Hz, 1 H), 7.11 (d, j = 2.5 Hz, 1 H), 6.35 (t, J =, 1 H), 5.05 (d, J = , 1 H), 4.47 (dd, J = 4.6 and 11 Hz, 1 H), 4.10-4.35 (mult, 2H),3.91 (s, 3 H), 3.88 (q, J = 7.2 Hz, 1 H), 3.04 (dd, J = 6.3 ands 13.6 Hz, 1 H), 2.88-2.95 (mult, 1 H), 1.56 (d, J = 7.2 Hz, 3 H), 1.39 (s, 9 H), 1.19 (s, 3 H), 1.17 (s, 3H). Anal calcd for $C_{26}H_{36}N_2O_6S$: C, 61.88; H, 7.19; N, 5.55; S, 6.35. Found: C, 62.14; H, 7.07; N, 5.20; S, 6.02.

21b. 3-(2-S-Nitroso-2-methyl propionic acid propyl amide)-2-amino-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) propyl ester hydrochloride

The product of Example 21a (500 mg, 1.0 mmol) and tert-butyl nitrite (150 μL, 1.2 mmol) were dissolved in methylene chloride (8 mL) and stirred at room temperature for 1.5 hour. The solvent was evaporated and the residue was filtered through a plug of silica gel to give 470 mg of nitrosothiol. The amine protecting group was removed by stirring in 3N HCl in EtOAc (6 mL) for 1 hour. The solvent was evaporated to give 330 mg (69 % overall) of the title compound as a green solid. ^{1}H-NMR ($CDCl_3$) δ: 9.00 (t, J = 6.0 Hz, 1 H), 8.5 (br s, 3 H), 7.78 (d, J = 8.9 Hz, 1 H), 7.76 (d, j = 8.5 Hz, 1 H), 7.20 (s, 1 H), 7.39 (dd, J = 1.8 and 8.5 Hz, 1 H), 7.14 (dd, J = 2.5 and 8.9 Hz, 1 H), 4.49 (pent. J = 6.5 Hz, 1 H), 4.14-4.22 (mult, 2 H), 3.87-3.97 (mult , 2 H), 3.85 (s, 3 H), 3.72 (dd, J = 5.6 and 13.9 Hz, 1 H), 1.78/1.80/1.89/1.97 (s, 6 H), 1.45 (d, J = 7.2 Hz, 3H).

Example 22

4-((2-S-Nitroso-2-methyl)-propyl amide)-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) butyl ester

22a. 3-Carboxy-propionic acid-(2-mercapto-2-methyl)-propyl amide

To a solution of succinic anhydride (15 g, 0.15 mol), pyridine (54 g, 0.69 mol), isopropyl alcohol (50 ml), and methylene chloride (150 ml) was added 1-amino-2-methyl-2 propanethiol hydrochloride (23.3 g, 0.16 mol) and the reaction was stirred at room temperature for 4 hours. The reaction was concentrated in vacuo and the residue partioned between ethyl acetate and 1N HCl. The organic phase was dried over sodium sulfate and the volatiles evaporated. The residual oil was recrystalized from ethyl acetate/hexane to afford the product as colorless prisms (22.3g, 73% yield). ^{1}H-NMR ($CDCl_3$) : δ 6.20 (br s, 1 H), 3.35 (d, J = 6.2 Hz, 2 H), 2.74 (m, 2 H), 2.58 (m, 2 H), 1.35 (s, 6H).

22b. 4-Hyroxy-butyric acid-(2-mercapto-2-methyl)-propyl amide

To a solution of the product of Example 22a (1.20 g 5.8 mmol) in anhydrous tetrahydrofuran (10 ml) was added borane dimethylsulfide complex (656 μl, 6.8 mmol) and the reaction mixture was allowed to stand at room temperature for 6 hours. The reaction mixture was concentrated in vacuo and the residue partioned between ethyl acetate and 1N HCl. The organic phase was dried over sodium sulfate to afford the crude product which was used without further purification. ^{1}H-NMR ($CDCl_3$) δ: 6.16 (br s, 1 H), 3.71 (t, J = 5.7 Hz, 2 H), 3.33 (d, J = 6.2 Hz, 2H) 2.41 (t, J = 6.8 Hz, 2 H), 1.63 (m, 2H) 1.30 (s, 6H).

22c. 4-((2-Mercapto-2-methyl)-propyl amide)-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) butyl ester

The product of Example 7a (0.204 g, 0.82 mmol) was dissolved in anhydrous methylene chloride (2 mL) and pyridine (66 μL, 0.82 mmol) was added. The reaction

mixture was cooled to -78°C and a solution of the product of Example 22b (0.187 g. 0.98 mmol) in anhydrous methylene chloride (3 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent was evaporated and the residue was purified by flash chromatography on silica gel eluting with hexane/ethyl acetate (1:1) to give 0.190g (59 % yield) of the product as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 6 H), 1.53-1.58 (d, 3 H), 1.86-1.95 (m, 2 H), 1.98-2.08 (m, 2 H), 3.15-3.21 (dd, 2 H), 3.80-3.87 (q, 1 H), 3.88 (s, 3 H), 4.02-4.18 (m, 2 H), 5.74 (s, 1 H), 7.07-7.10 (d, 1 H), 7.10-7.15 (dd, 1 H), 7.38-7.43 (dd, 1 H), 7.65 (s, 1 H), 7.65-7.69 (d, 1 H), 7.69-7.72 (d, 1 H).

22d. 4-((2-S-Nitroso-2-methyl)-propyl amide)-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) butyl ester

The product of Example 22c (0.102 g, 0.26 mmol) was dissolved in anhydrous methylene chloride (2 mL) and tert-butyl nitrite (46 μL, 0.39 mmol) was added. The reaction mixture was stirred for 15 minutes at room temperature and the solvent was evaporated in vacuo to give 0.105 g (93 % yield) of the title compound as a green oil. ^{1}H NMR ($CDCl_3$) δ 1.53-1.59 (d, 3 H), 1.78 (s, 6 H), 1.81-1.99 (m, 4 H), 3.79-3.86 (q, 1 H), 3.86-3.90 (dd, 2 H), 3.91 (s, 3 H), 3.97-4.18 (m, 2 H), 5.41 (s, 1 H), 7.07-7.10 (d, 1 H), 7.10-7.15 (dd, 1 H), 7.36-7.40 (dd, 1 H), 7.65-7.70 (d, 3 H).

Example 23

2-((2-S-Nitroso-2-methyl) propyl amide)-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) ethyl ester

23a. Chloroacetic acid (2-tetrahydropyranyl thioether-2-methyl-propyl)-amide

To a stirred solution of pyridine (2.37 g, 30 mmol), 1-amino-2-methyl-2 propanethiol hydrochloride (2 g, 14 mmol in methylene chloride (30 ml) at 0 °C was added dropwise chloroacetyl chloride (1.7 g, 15 mmol). After the addition was complete and the reaction mixture was stirred overnight with slow warming to room temperature. The reaction was washed with 4N HCl and the organic phase was dried

over sodium sulfate and then concentrated in vacuo. A portion of the residue (0.370g. 2.04 mmol) was combined with dihydropyran (326 μL, 2.24 mmol) and cooled to 0°C. A 4M solution of hydrochloric acid in ethyl ether (14 μL) was added and the reaction mixture was stirred for 3 hours at room temperature. The solvent was evaporated in vacuo to give 0.530 g (98 % yield) of the product as a colorless oil. ^{1}H NMR ($CDCl_3$) δ: 1.23-1.42 (d, 6 H), 1.51-1.73 (m, 4 H), 1.74-1.91 (m, 2 H), 3.23-3.35 (dd, 1 H), 3.42-3.58 (m, 2 H), 4.05 (s, 2 H), 4.05-4.11 (dd, 1 H), 4.81-4.89 (dd, 1 H), 7.54 (s, 1 H).

23b. 2-((2-tetrahydropyranyl thioether 2-methyl) propyl amide)-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) ethyl ester

Under a nitrogen atmosphere (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid sodium salt (0.514 g, 2.04 mmol) was suspended in anhydrous dimethylformamide (10 mL) and a solution of the product of Example 23a (0.519 g, 2.04 mmol) in anhydrous dimethylformamide (5 mL) was added. The reaction mixture was stirred for 17 hours at room temperature. The solvent was evaporated, the residue was suspended in methylene chloride, and the precipitate was filtered. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography on silica gel eluting with hexane/ethyl acetate (2:1) to give 0.263 (28 % yield) of the the product as an oil. ^{1}H NMR (CDCl) δ: 1.06-1.15 (d, 3 H), 1.23-1.26 (d, 3 H), 1.43-1.59 (m, 4 H), 1.60-1.66 (d, 3 H), 1.51-1.84 (m, 2 H), 3.04-3.22 (ddd, 1 H), 3.24-3.48 (m, 2 H), 3.87 (s, 3 H), 3.91-4.03 (m, 2 H), 4.41-4.64 (m, 2 H), 4.70-4.76 (m, 1 H), 6.94-7.05 (m, 1 H), 7.06-7.10 (d, 1 H), 7.11-7.15 (dd, 1 H), 7.37-7.46 (dd, 1 H), 7.63-7.71 (m, 3 H).

23c. 2-((2-Mercapto-2-methyl) propyl amide)-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) ethyl ester

The product of Example 23b (0.180 g, 0.39 mmol) was dissolved in methanol and a solution of silver nitrate (0.133g, 0.79 mmol) in water (0.5 mL) was added. The reaction mixture was stirred for 30 minutes at room temperature and the solvent

was evaporated. The residue was suspended in dichloromethane (50 mL) and a 4M solution of hydrochloric acid in ethyl ether (1 mL) was added. After 12 hours stirring at room temperature, the precipitate was filtered, the filtrate washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated and the residue was purified by flash chromatography on silica gel eluting with hexane/ethyl acetate (3:1) to (1:1) to give 0.046 g (31 % yield) of the title compound (2c) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ: 1.01-1.11 (d, 6 H), 1.19 (s, 1 H), 1.59-1.64 (d, 3 H), 2.94-3.03 (dd, 1 H), 3.15-3.24 (dd, 1 H), 3.90 (s, 3 H), 3.91-4.00 (q, 1 H), 4.43-4.50 (d, 1 H), 4.70-4.77 (d, 1 H), 6.13 (s, 1 H), 7.07-7.11 (d, 1 H), 7.12-7.17 (dd, 1 H), 7.37-7.44 (dd, 1 H), 7.65-7.74 (m, 3 H).

23d. 2-((2-S-Nitroso-2-methyl) propyl amide)-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) ethyl ester

The product of Example 23c (0.040 g, 0.11 mmol) was dissolved in anhydrous methylene chloride (1 mL) and tert-butyl nitrite (19 μL, 0.16 mmol) was added. The reaction mixture was stirred for 15 minutes at room temperature and the solvent was evaporated in vacuo to give 0.043 g (100 % yield) of the title compound as a green oil. ^{1}H NMR ($CDCl_3$) δ: 1.54 (s, 3 H), 1.56-1.61 (t, 6 H), 3.59-3.68 (dd, 1 H), 3.92 (s, 3 H), 3.82-3.91 (m, 2 H), 4.02-4.46 (d, 1 H), 4.69-4.75 (d, 1 H), 5.90 (s, 1 H), 7.09-7.12 (d, 1 H), 7.13-7.18 (dd, 1 H), 7.29-7.34 (dd, 1 H), 7.61-7.71 (m, 3 H).

Example 24

3-S-Nitro-3-methyl-1-(3-benzoyl-α-methylbenzeneacetic acid) butyl ester

To a solution of the product of Example 6a (103 mg, 0.29 mmol) in methylene chloride (3 ml) was bubbled in dinitrogen tetroxide till saturation. The reaction mixture was allowed to stand at room temperature for 20 minutes and the the excess dinitrogen tetroxide was blown off by bubbling nitrogen gas through the solution. The volatiles were evaporated and the residue purified by flash silica gel chromatography eluting with ether/hexanes (2:1) to afford 93.7 mg (80 %) of the title compound as a colorless oil.

^{1}H NMR ($CDCl_3$) δ:_1.44 (s, 3 H), 1.45 (s, 3 H), 1.53 (d, J = 7.0 Hz, 3 H), 1.69 (br s, 1 H), 2.26 (t, J = 6.4 Hz, 2 H), 3.78 (q, J = 7.0 Hz, 3 H), 4.23 (td, J = 6.35 Hz, J = 2.25 Hz, 2 H), 7.4-7.8 (m, 9H).

Example 25

5-(1, 3-(2-S-Nitroso-2-methyl)-dipropyl amide)-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) isophthalic ester

25a. 5-Acetoxyisophthalic acid

To a stirred solution of isophthalic acid (2.0 g, 11.0 mmol) in pyridine (10 ml) was added acetic anhydride 1.23 g, 12.1 mmol) and the reaction was allowed to stir at room temperature for 3 hours. The reaction mixture was concentrated in vacuo and the residue partioned between ethyl acetate and 2N HCl. The organic phase was dried over sodium sulfate and the volatiles evaporated to afford 2.17 g (88 %) of the product as a white solid. ^{1}H NMR ($CDCl_3$/DMSO) δ:2.33 (s, 3 H), 7.71 (m, 2 H), 8.60 (m, 2 H).

25b. 5-Acetoxy-(1, 3-(2-mercapto-2-methyl)-dipropyl) amide

To a solution of the product of Example 25a (506 mg, 2.26 mmol) in anhydrous tetrahydrofuran (6 ml) was added dimethylformamide (1 drop) and oxalyl chloride (631 mg, 5 mmol) and the reaction mixture was stirred at room temperature for 15 minutes. Concentration of the volatiles in vacuo folloed by azeotroping the residue with additional tetrahydrofuran (2 x 5 ml) afforded the crude acid chloride which was used without further purification in the next step. To a solution of 2-amino-2-methyl-2-propanethiol hydrochloride (720 mg, 5 mmol), pyridine (2.34 g, 29 mmol) in methylene chloride (10 ml) was added the acid chloride in methylene chloride (5 ml) and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was concentrated in vacuo and the residue partioned between methylene chloride and 1N HCl-brine. The organic phase was dried over sodium sufate and the volatiles evaporated to afford 693 mg (82 %) the crude product as a white solid. ^{1}H NMR ($CDCl_3$) δ:_1.43

(s, 12 H), 1.71 (s, 2 H), 2.36 (s, 3 H), 3.55 (d, J = 6.2 Hz, 4 H), 6.80 (m, 2 H), 7.27 (s, 2 H), 7.71 (d, J = 1.5 Hz, 1 H).

25c. 5-Hydroxy-1, 3-(2-mercapto-2-methyl)-dipropyl amide

To the product of Example 25b (690 mg, 1.8 mmol) in methanol (10 ml) was added lithium hydroxide monohydrate (90 mg, 2.1 mmol) and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated in vacuo and the residue partioned between ethyl acetate and 1N HCl-brine. The organic phase was dried over sodium sulfate and and the volatiles evaporated to afford 540 mg (90 %) of the crude product as a white solid. ^{1}H NMR ($CDCl_3$) δ:1.42 (s, 12 H), 1.71 (s, 2 H), 3.53 (d, J = 6.1 Hz, 4 H), 6.92 (m, 2 H), 7.62 (s, 2 H), 7.74 (s, 1 H).

25d. 5-(1, 3-(2-Mercapto-2-methyl)-dipropyl amide)-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) isophthalic ester

To a stirred solution of (S)-6-methoxy-α-methyl-2-naphthaleneacetic acid (69 mg, 0.30 mmol) in tetrhydrofuran (2 ml) at 0°C was added triethylamine (32 mg, 0.32 mmol) and isobutyl chloroformate (40 mg, 0.30 mmol) and the reaction mixture was stirred for an additional 10 minutes. The product of Example 25c (100 mg, 0.30 mmol) and pyridine (5 ml) were added and the reaction mixture stirred at room temperature for 18 hours. The reaction mixture was concentrated in vacuo and the residue purified by flash silica gel chromatography to afford 22 mg (13 %) of the product as a white solid. ^{1}H NMR ($CDCl_3$) δ:1.38 (s, 12 H), 1.52-1.74 (m, 5 H), 3.48 (d, J = 6.1 Hz, 4 H), 3.91 (s, 3 H), 4.12 (q, J = 7.0 Hz, 1 H), 6.73 (m, 2 H), 7.18 (m, 2 H), 7.48 (d, J = 7.2 Hz, 1 H), 7.50 (s, 2 H), 7.58-7.77 (m, 3 H), 8.05 (s, 1 H).

25e. 5-(1, 3-(2-S-Nitroso-2-methyl)-dipropyl amide)-1-((S)-6-methoxy-α-methyl-2-naphthaleneacetic acid) isophthalic ester

The product of Example 25d (0.018 g, 0.032 mmol) was dissolved in anhydrous methylene chloride (1 mL) and cooled to 0°C. Tert-butyl nitrite (20 μL, 0.17 mmol)

was added and the resulting mixture was stirred for 25 minutes. The solvent was evaporated in vacuo to give 0.018 g (90 % yield) of the title compound as a green solid. ^{1}H NMR ($CDCl_3$) δ: 1.66-1.73 (d, 3 H), 1.89 (s, 12 H), 3.93 (s, 3 H), 4.04-4.13 (q, 1 H), 4.15-4.19 (d, 4 H), 6.54-6.58 (t, 2 H), 7.15 (s, 1 H), 7.16-7.19 (d, 1 H), 7.42-7.48 (m, 3 H), 7.70-7.80 (m, 4 H).

Example 26

Comparative *In Vivo* Analgesic, Antiinflammatory and Gastric Lesion Activities

The phenylbenzoquinone-induced writhing test in mice was used to measure analgesic activity. The ability of the compounds to inhibit phenylbenzoquinone-induced writhing in mice was measured using the method of Siegmund *et al., Proc. Soc. Exp. Biol. Med. 95*: 729-731, 1957. Male CD-1 mice (Charles River Laboratories, Wilmington, MA) weighing 20-25 g were fasted overnight. Vehicle or compounds were administered by oral gavage 1 hour prior to i.p. injection of 2 mg/kg of phenylbenzoquinone. In the case of a nitric oxide adduct being given in combination with a NSAID, the nitric oxide adduct was administered immediately before the NSAID. Five minutes after the i.p. injection of phenylbenzoquinone, the number of writhes in a 5 minute period was counted.

The rat paw edema test was used to measure antiinflammatory activity. The rat paw edema test was performed according to the method of Winter *et al., Proc. Soc. Exp. Biol. Med. 111*: 544-547, 1962. Male Sprague-Dawley rats (250-275 g) were fasted overnight and dosed by oral gavage with vehicle or suspensions of compound one hour prior to the subplantar injection of 50 μl of 1 % suspension of carrageenin. Three hours later, the paw volume was measured and compared with the initial volume measured immediately after carrageenin injection.

The rat gastric lesion test (Kitagawa *et al.*, *J. Pharmacol. Exp.Ther.*, *253*:1133-1137, 1990; Al-Ghamdi *et al.*, *J. Int. Med. Res.*, *19*: 2242, 1991) was used to evaluate the potential of compounds to produce gastric lesion. Male Sprague Dawley rats (Charles River Laboratories, Wilmington, MA) weighing 230-250 g were used for the experiments. The rats were housed with laboratory chow and water *ad libitum* prior to the study. The rats were fasted for 24-30 hours with free access to water and then dosed by oral gavage with vehicle or with drugs given at a volume of 0.5 mL/100 g. For the unmodified NSAIDs being given in combination with a nitric oxide adduct (NO-adduct), the NO-adduct was administered by oral gavage immediately prior to the administration of NSAID by oral gavage. Food was withheld for 18 hours after the inital dosing. For acute studies, rats were euthanized by CO_2 eighteen hours after dosing and the stomachs were dissected. For the multiple dosing studies, the results of which are in Table 3, food was given eighteen hours after the first dose and the rats were maintained on food and water *ad libitum* while receiving a single daily dose for the remainder of the experiment. For the multiple dosing studies, the results of which are in Table 4, the rats were either fasted 24-30 hours before the first dosing and for 4 hours after the first dosing, (4 day study with ketoprofen, Example 4, and Example 6); allowed access to food and water *ad libitum* before as well as during the experiment, (7 day study with ketoprofen and Example 4); or fasted 24-30 hours prior to the first dosing and for 18 hours after the first dosing, (7 day study with ibuprofen, Example 11, and Example 12). The stomachs were dissected along the greater curvature, washed with a directed stream of 0.9% saline and pinned open on a sylgard based petridish for examination of the hemorrhagic lesion. Gastric lesion score was expressed in mm and calculated by summing the length of each lesion.

Table 1 shows the relative activities of compounds in the analgesic, antiinflammatory and gastric lesion tests, and are expressed, for each novel NSAID compound, as described according to the general formulas (I), (II), (III) and (IV), or NSAID coadministered with an NO-adduct, as the ratio of activitiy relative to the parent NSAID.

Table 1

	Relative Activity		
Compound	Analgesia	Antiinflammation	Gastric Lesion
Ketoprofen	1	1	1
Example 4	1.6	0.7	0.03
Example 6	1	ND	ND
Example 5	1.1	ND	ND
Example 16	1.1	ND	ND
Flurbiprofen	1	1	1
Example 13	0.31	1.83	0.5
Indomethacin	1	1	1
Example 8	1	1	0.08
Ibuprofen	ND	1	1
Example 12	ND	1	<0.03
Example 11	ND	1	<0.05
Piroxicam	1	ND	1
Piroxicam + Example 2	1.3	ND	0.08

ND - not determined

Table 2 shows the results of single dose treatment studies in which various NO-adducts were administered in combination with various NSAIDs. The combinations are able to protect against the NSAID induced gastric toxicity.

Table 2

NSAID	(mg/kg)	NO-Adduct	Molar Dose Ratio NSAID : NO-Adduct	Gastric Lesion Protection
Piroxicam	16	Example 2	1 : 1	+++
Piroxicam	8	Example 2	1 : 1	+++
Piroxicam	8	Isoamyl nitrite	1 : 3	+++
Piroxicam	8	Isosorbide dinitrate	1 : 3	+++
Piroxicam	8	Example 1	1 : 2	++
Flurbiprofen	16	Example 2	1 : 1	++
Tenidap	16	Example 2	1 : 1	++
Indomethaacin	20	Example 2	1 : 1	++
Tenidap	22.5	Example 1	1 : 1	+++

70-100% Protection = +++; 40-69% Protection = ++; 20-39% Protection = +

Table 3 shows the results of multiple dose treatment studies in which various NO-adducts were administered in combination with various NSAIDs. The combinations are able to protect against the NSAID induced gastric toxicity.

Table 3

Treatment (Days)	NSAID	(mg/kg)	Molar Dose Ratio NO-Donor	Gastric Lesion NSAID : NO-Adduct	Protection
3	Piroxicam	16	Example 2	1 : 1	+++
14	Piroxicam	16	Example 2	1 : 1	++
7	Ibuprofen	40	Example 2	1 : 1	+
14	Ibuprofen	30	Example 2	1 : 1	++

70-100% Protection = +++; 40-69% Protection = ++; 20-39% Protection = +

Table 4 shows the results of multiple dose treatment studies in which various novel NSAID compounds directly or indirectly linked to various NO-adducts were administered. The modified NSAIDs containing NO-adducts produced significantly less gastric toxcity.

Table 4

Compound	(mg/kg)	Treatment (Days)	Relative Gastric Lesion Activity
Ketoprofen	10	4	+++++
Example 4	14	4	+
Example 6	15	4	++
Ketoprofen	10	7	+++++
Example 4	14	7	+
Ibuprofen	30	7	+++++

Example 11	50	7	+
Example 12	45	7	+
Vehicle		7	+

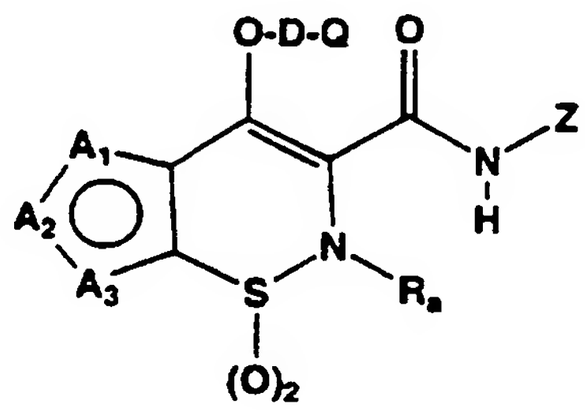
100% of the gastric toxcity induced by the parent NSAID = +++++
21-40% of the gastric toxcity induced by the parent NSAID = ++
1-20% of the gastric toxcity induced by the parent NSAID = +

What Is Claimed Is:

1. A non-steroidal antiinflammatory agent to which is directly or indirectly linked at least one NO group.

2. The non-steroidal antiinflammatory agent of claim 1 which is selected from the group consisting of:

(i) compounds having the structure



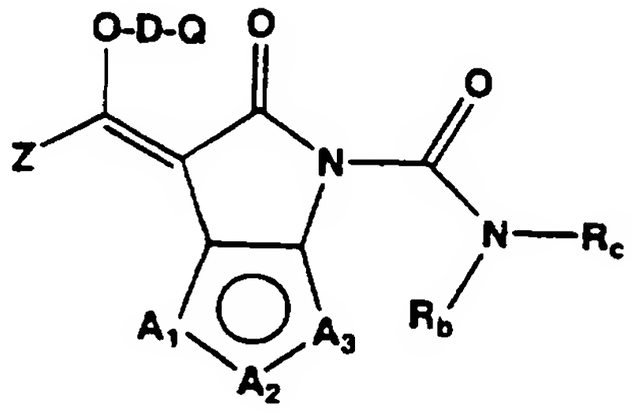
I

wherein

D is selected from (i) a covalent bond; (ii) $-C(R_a)-O-C(O)-Y-[C(R_b)(R_c)]_p-T$ in which R_a is lower alkyl, cycloalkyl, aryl or heteroaryl, Y is oxygen, sulfur, or NR_i in which R_i is hydrogen or lower alkyl, R_b and R_c are independently selected from, hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, aminoarylalkyl, alkylamino, dialkylamino or taken together are cycloalkyl or bridged cycloalkyl, p is an integer from 1 to 6 and T is a covalent bond, oxygen, sulfur, or nitrogen and Q is -NO or $-NO_2$ with the proviso that -T-Q is not $-O-NO_2$; or (iii)$-(CO)-T_1-[C(R_b)(R_c)]_p-T_2$ wherein T_1 and T_2 are independently selected from T, and wherein R_b, R_c, p and T are as defined above and with the provision that -T-Q does not equal $-O-NO_2$; Z is an aryl or heteroaryl; and A_1, A_2 and A_3 comprise the other subunits of a 5- or 6-membered monocyclic aromatic ring and each is independently selected from (1) $C-R_1$ wherein R_1 at each occurrence is independently selected from hydrogen, lower alkyl, lower haloalkyl, alkoxyalkyl, halogen or nitro; (2) $N-R_d$ wherein R_d at each occurrence is independently selected from a covalent bond to an adjacent ring atom in order to render the ring aromatic, hydrogen, lower alkyl, cycloalkyl, arylalkyl, aryl, heteroaryl; (3) sulfur; (4) oxygen; and (5)

$B_a=B_b$ wherein B_a and B_b are each independently selected from nitrogen or C-R_1 wherein at each occurrence R_1 is as defined above;

(ii) compounds having the structure

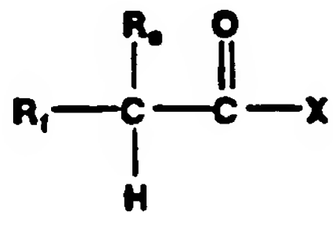


II

wherein

R_b, R_c, D, Q, Z, A_1, A_2 and A_3 are as defined above;

(iii) compounds having the structure

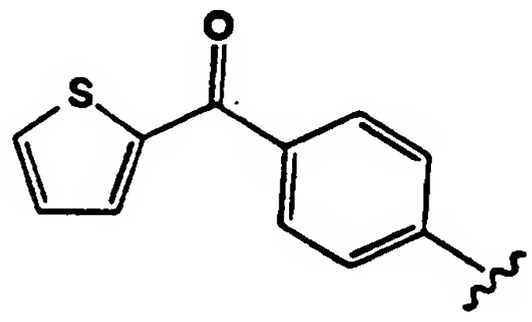


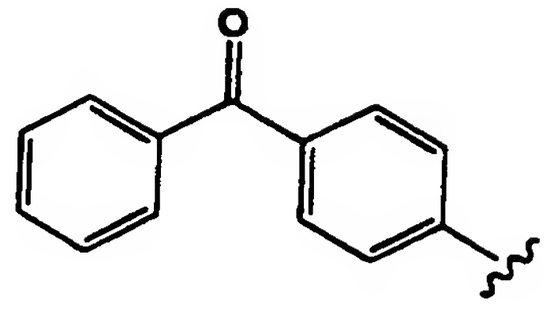
III

wherein

R_c is hydrogen or lower alkyl;

R_f is selected from

(1) 

(2) 

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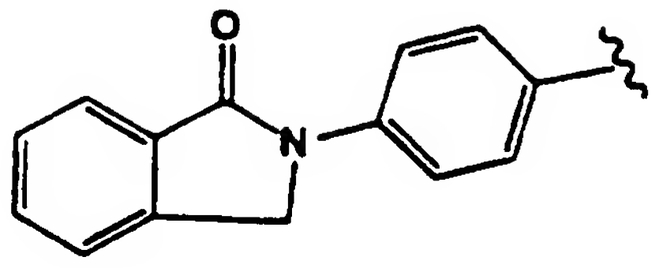

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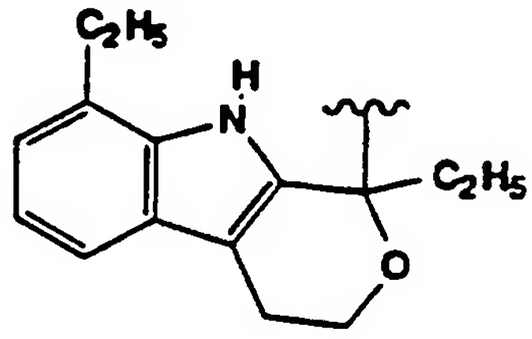

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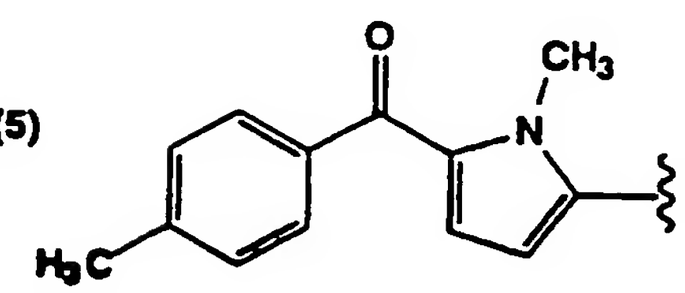

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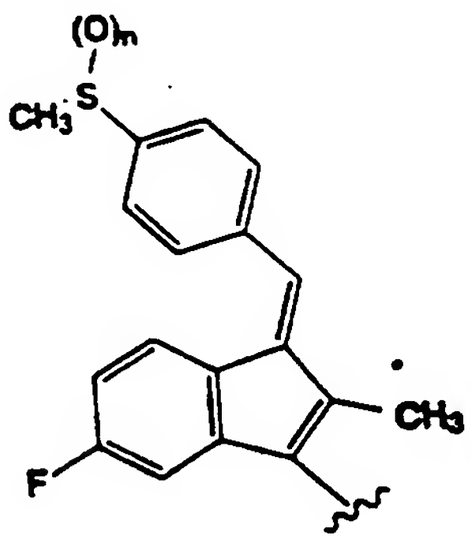

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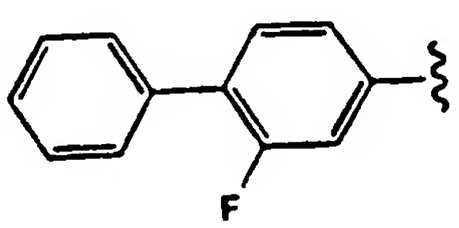

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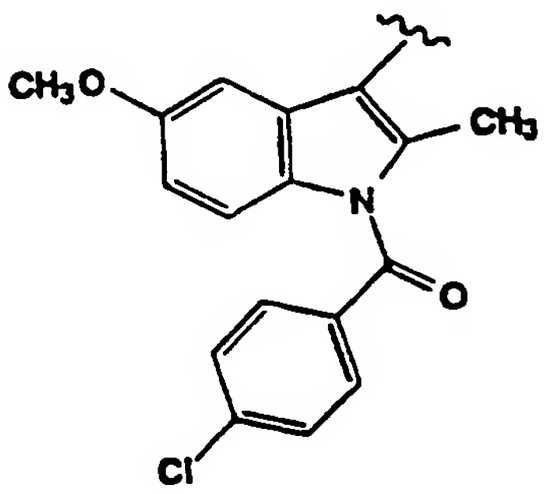

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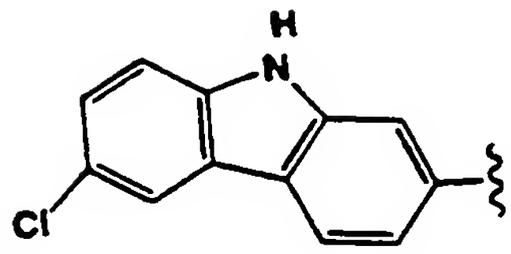

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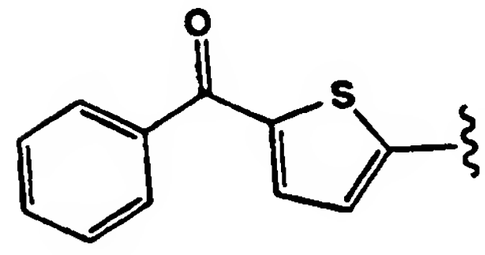

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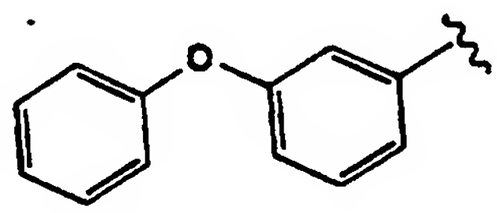

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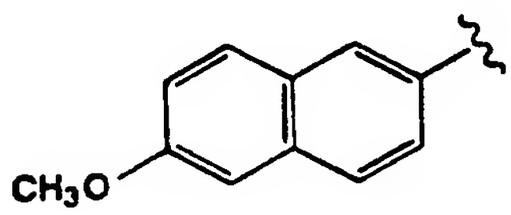

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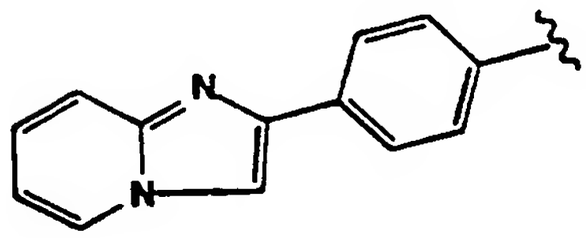

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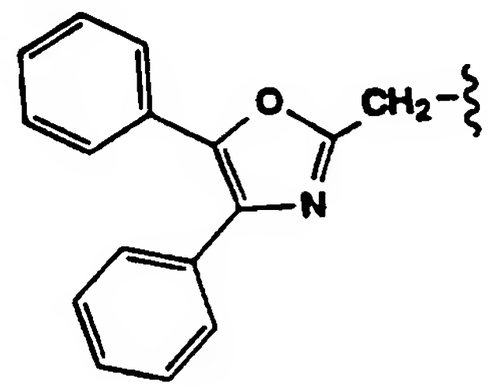

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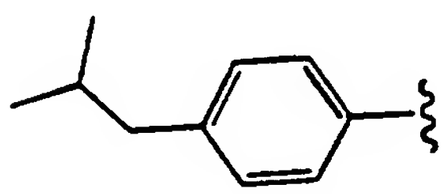
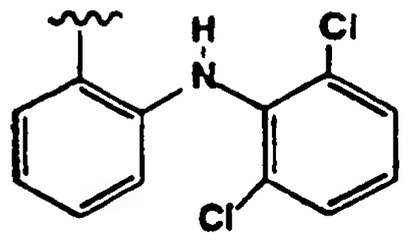
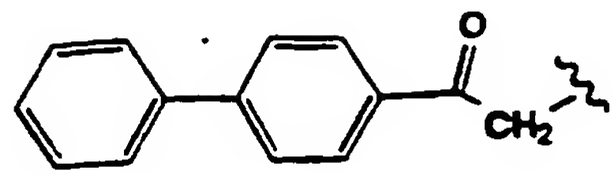
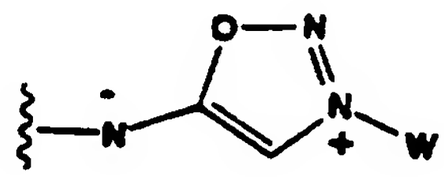


(16) 

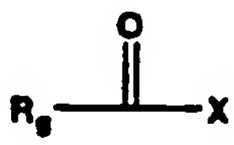
(17) 

in which n is 0 or 1; and

X is (1) -Y-[$C(R_b)(R_c)$]p_1-G-[$C(R_b)(R_c)$]p_2-T-Q, wherein G is (i) a covalent bond; (ii) -T-C(O)-; (iii) -C(O)-T; (iv) -C(Y-C(O)-R_m)- wherein R_m is heteroaryl or heterocyclic ring; p_1 and p_2 are independently selected from p and in which Y, R_b, R_c, p and T are as defined above with the proviso that -T-Q is not -O-NO_2; (2)



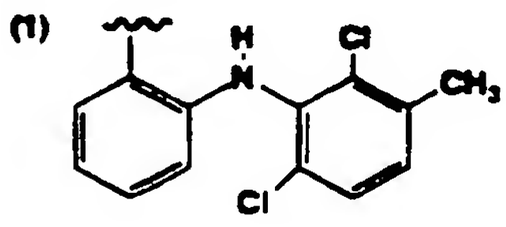
in which W is a heterocyclic ring or NR_hR_i wherein R_h and R_i are independently selected from lower alkyl, aryl or alkenyl; (3) -Y_1[$C(R_b)(R_c)$]$_s$-Z-[C(O)-Y_2-[$C(R_b)(R_c)$]$_{P1}$-T-Q]$_{P2}$ wherein Y_1, and Y_2 are independently selected from Y, S is an integer from 0 to 3, and R_b, R_c, Z, T, and Q are as defined above with the proviso that -T-Q is not is -O-NO_2; and compounds having the structure

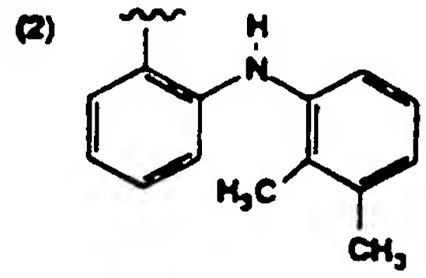


XV

wherein

R_g is selected from

(1) 

(2) 

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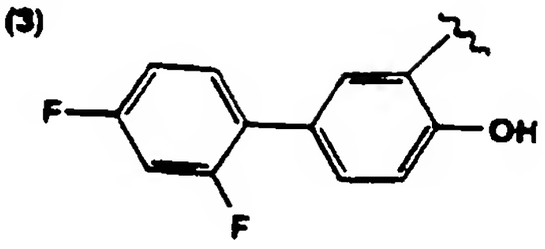

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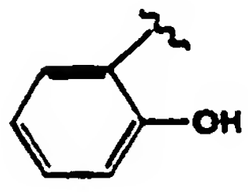

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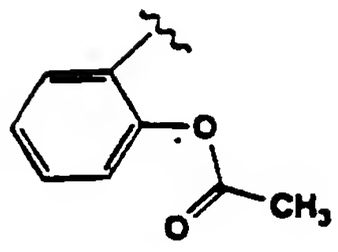

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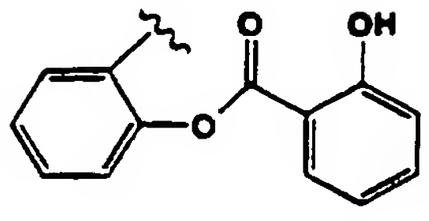

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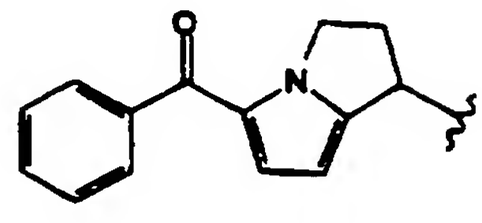


and X is defined as above.

3. A composition comprising (i) a therapeutically effective amount of a nonsteroidal antiinflammatory drug and (ii) an NSAID toxicity reducing amount of a compound that donates nitric oxide, transfers nitric oxide, releases nitric oxide, or elevates endogenous synthesis levels of nitric oxide.

4. The composition of claim 3 wherein the nonsteroidal antiinflammatory drug is selected from the group consisting of salicylic acid derivatives, pyrazolon derivatives, para-aminophenol derivatives, indole derivatives, fentamates, tolmetin, propionic acid derivatives, oxicam derivatives, phenylacetic acid derivatives, cytokine inhibitors, cyclooxygenase inhibitors and selective cyclooxygenase-1 inhibitors as well as cyclooxygenase-2 inhibitors.

5. The composition of claim 4 wherein the salicylic acid derivatives are selected from the group consisting of acetylsalicylic acid, diflunisal, salsalate, sodium salicylate, salicylamide, sodium thiosalicylate, choline salicylate, magnesium salicylate, mesalamine, sulfasalazine and methylsalicylate; the pyrazolon derivatives are selected from the group consisting of phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, dipyrone and apazone; the para-aminophenol derivatives are selected from the group consisting of phenacetin and acetaminophen; the indole derivatives are selected

from the group consisting of indomethacin and sulindac; the fenamates are selected from the group consisting of mefenamic, meclofenamic, flufenamic, tolfenamic and etofenamic acids and pharmaceutically acceptabl salts thereof; the propionic acid derivatives are selected from the group consisting of ibuprofen, naproxen, flurbiprofen, fenoprofen, ketoprofen, fenbufen, miroprofen, corprofen, pirprofen, oxaprozin, indoprofen and tiaprofenic acid and pharmaceutically acceptable salts thereof; the oxicam derivatives are selected from the group consisting of piroxicam, isoxicam, amperoxicam tenoxicam and the related compound tenidap; the phenylacetic acid derivative is tolmetin or diclofenac and pharmaceutically acceptable salts thereof; the cyclooxygenase inhibitors are selected from the group consisting of etodolac and nabumetone; the selective cyclooxygenase-2 inhibitors are selected from the group consisting of CGP 28238 (6-(2,4-difluorophenoxy)-5-methyl-sulfonylamino -1-indanone), SC-58125 (1-[(4-methylsulfonyl)phenyl]-3- trifluoromethyl-5-(4-fluorophenyl)pyrazole), NS-398 (N-[2-(cyclohexyloxy)-4-nitro-phenyl]methanesulfonamide), DuP 697 (5-bromo-2(fluorophenyl)-3-(4-methylsulfonylphenyl) thiophene), L-745,337 (5-methanesulphonamida-6-(2,4-diflurorthiophenyl)-1-indanone), the 1,2-substituted diarylcyclopentene analogues such as 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene; and the quinazolinone, such as proquazone.

6. The composition of claim 3 wherein the compound that donates, transfers or releases nitric oxide is a S-nitrosothiol.

7. The composition of claim 6 wherein the S-nitrosothiol is selected from the group consisting of those having the structures:

(i) $CH_3[C(R_b)(R_c)]_xSNO$

wherein x equals 2 to 20 and R_b and R_c are as defined above;

(ii) $HS[C(R_b)(R_c)]_xSNO$

wherein x equals 2 to 20; and

(iii) $ONS[C(R_b)(R_c)]_xV$

wherein x equals 2 to 20 and V is selected from the group consisting of fluoro, alkoxy, cyano, carboxamido, cycloalkyl, arylkoxy, alkylsulfinyl, arylthio, alkylamino, dialkylamino, hydroxy, carbamoyl, N-alkylcarbamoyl, N,N-dialkylcarbamoyl, amino, hydroxyl, carboxyl, hydrogen, nitro and aryl; and R_b and R_c are independently selected from, hydrogen, lower alkyl, cycloalkyl, aryl, hereroaryl, arylalkyl, alkylamino, dialkylamino or taken together are cycloalkyl or bridged cycloalkyl.

8. The composition of claim 3 wherein the compound that donates, transfers or releases nitric oxide is selected from the group consisting of:

(i) compounds that include at least one ON-O-, ON-N- or ON-C- group;

(ii) 2-hydroxy-2-nitrosohydrazine which has an $R_{100}R_{200}$-N(O-M^+)-NO group wherein R_1 and R_2 include polypeptides, amino acids, sugars, modified and unmodified oligonucleotides, hydrocarbons where the hydrocarbon can be a branched or unbranched, and saturated or unsaturated aliphatic hydrocarbon or an aromatic hydrocarbon, hydrocarbons having one or more substituent groups and heterocyclic compounds; and

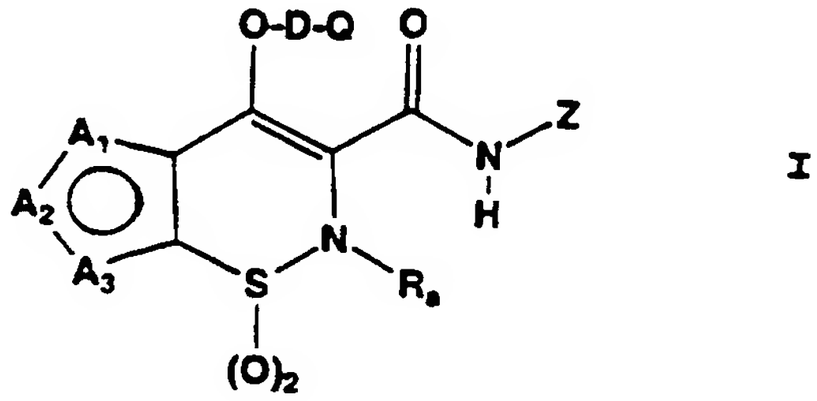
(iii) a thionitrate which has the structure R_{100}-(S)-NO_2 wherein R_{100} includes polypeptides, amino acids, sugars, modified and unmodified oligonucleotides, and a hydrocarbon where the hydrocarbon can be a branched or unbranched, and saturated or unsaturated aliphatic hydrocarbon or an aromatic hydrocarbon.

9. A composition comprising a non-steroidal antiinflammatory agent to which is directly or indirectly linked at least one NO group and a compound that donates nitric oxide, transfers nitric oxide, releases nitric oxide, or elevates endogenous synthesis levels of nitric oxide.

10. The composition of claim 9 wherein the nonsteroidal antiinflammatory drug is a compound which has been nitrosylated through a site selected from the group consisting of oxygen, sulfur, carbon and nitrogen.

11. The composition of claim 9 wherein the nitroso substituted compounds is selected from the group consisting of:

(i) compounds having the structure



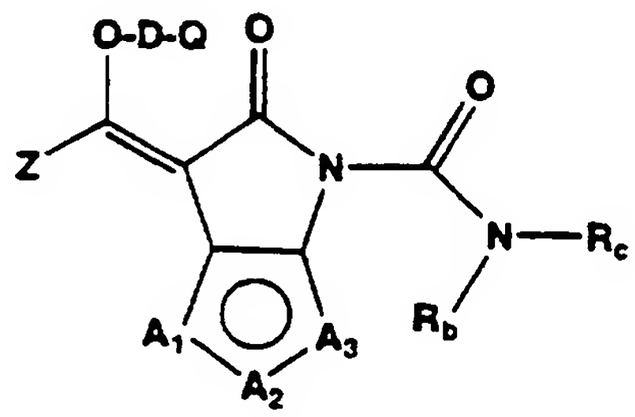
I

wherein

D is selected from (i) a covalent bond; (ii) $-C(R_a)-O-C(O)-Y-[C(R_b)(R_c)]_p-T$ in which R_a is lower alkyl, cycloalkyl, aryl or heteroaryl, Y is oxygen, sulfur, or NR_i in which R_i is hydrogen or lower alkyl, R_b and R_c are independently selected from, hydrogen, lower alkyl, cycloalkyl, aryl, heteroaryl, aminoarylalkyl, alkylamino, dialkylamino or taken together are cycloalkyl or bridged cycloalkyl, p is an integer from 1 to 6 and T is a covalent bond, oxygen, sulfur, or nitrogen and Q is -NO or $-NO_2$ with the proviso that -T-Q is not $-O-NO_2$; or (iii)$-(CO)-T_1-[C(R_b)(R_c)]_p-$ T_2 wherein T_1 and T_2 are independently selected from T, and wherein R_b, R_c, p and T are as defined above and with the provision that -T-Q does not equal $-O-NO_2$; Z is an aryl or heteroaryl; and A_1, A_2 and A_3 comprise the other subunits of a 5- or 6-membered monocyclic aromatic ring and each is independently selected from (1) $C-R_1$ wherein R_1 at each occurrence is independently selected from hydrogen, lower alkyl, lower haloalkyl, alkoxyalkyl, halogen or nitro; (2) $N-R_d$ wherein R_d at each occurrence is independently selected from a covalent bond to an adjacent ring atom in order to render the ring aromatic, hydrogen,

lower alkyl, cycloalkyl, arylalkyl, aryl, heteroaryl; (3) sulfur; (4) oxygen; and (5) $B_a=B_b$ wherein B_a and B_b are each independently selected from nitrogen or C-R_1 wherein at each occurrence R_1 is as defined above;

(ii) compounds having the structure

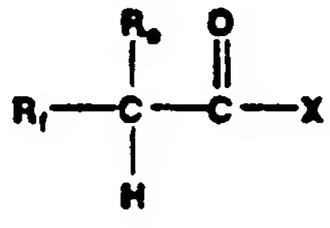


II

wherein

R_b, R_c, D, Q, Z, A_1, A_2 and A_3 are as defined above;

(iii) compounds having the structure



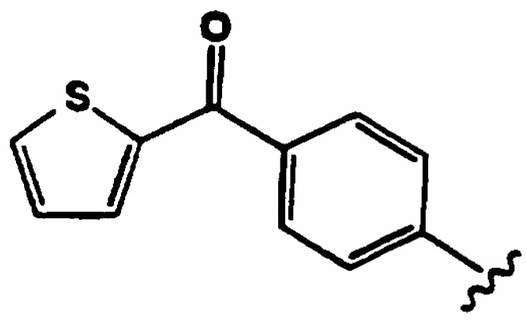
III

wherein

R_c is hydrogen or lower alkyl;

R_f is selected from

(1)



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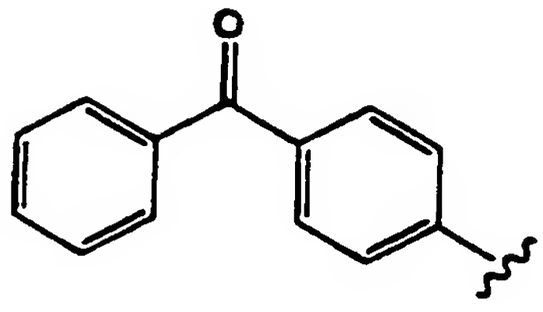

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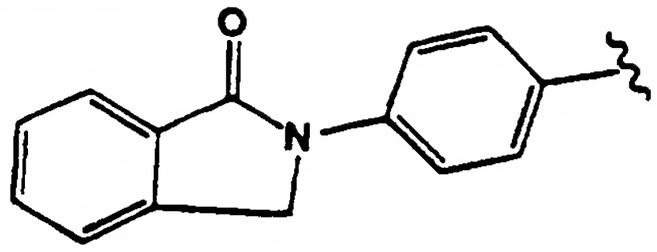

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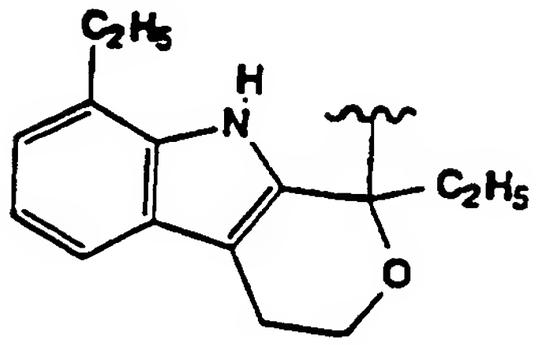

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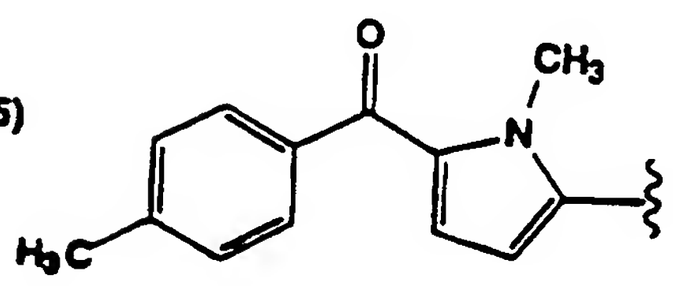

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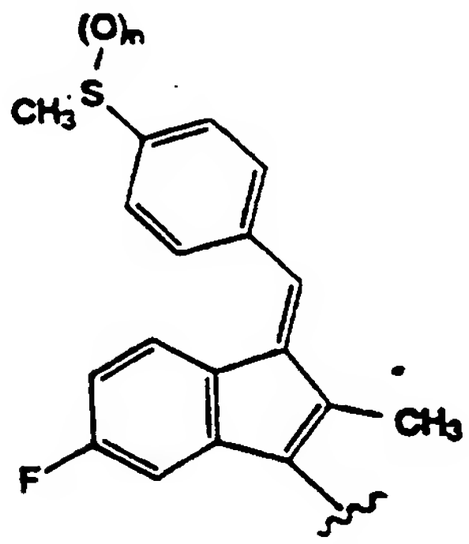

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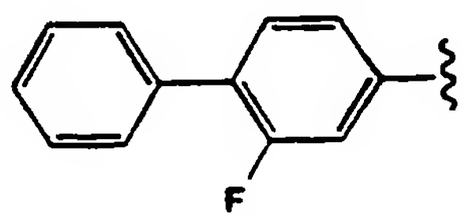

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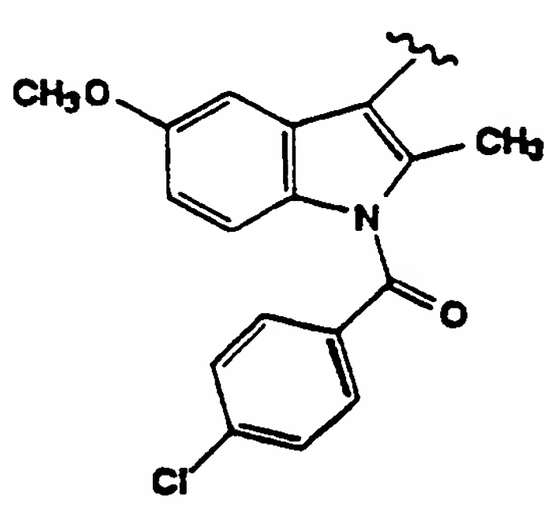

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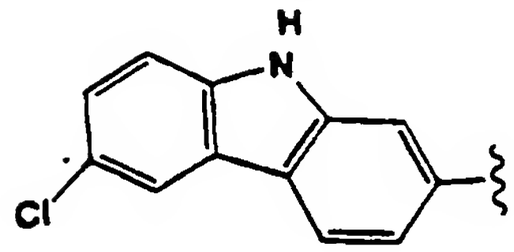

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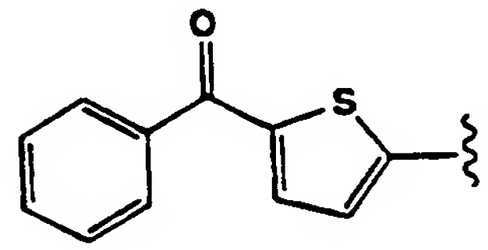

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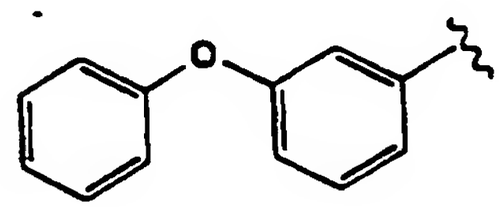

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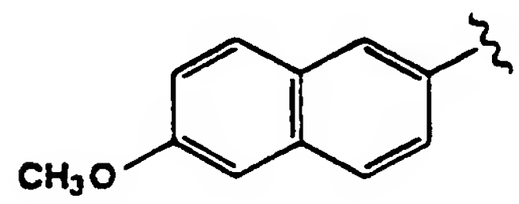

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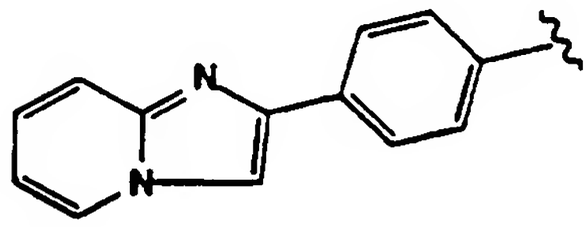

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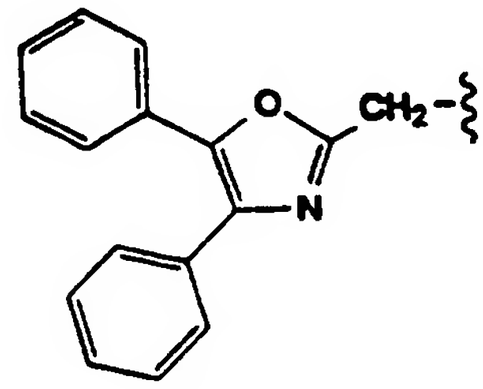

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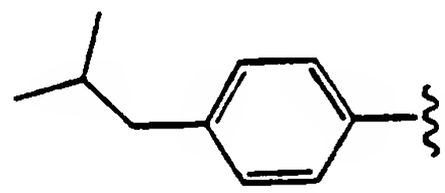
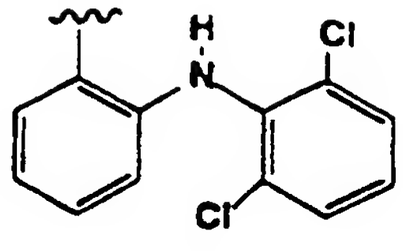
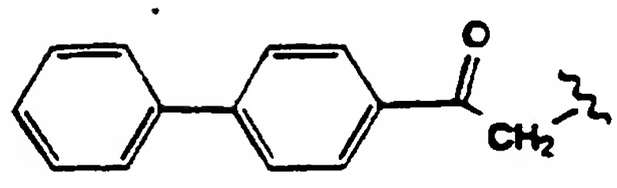
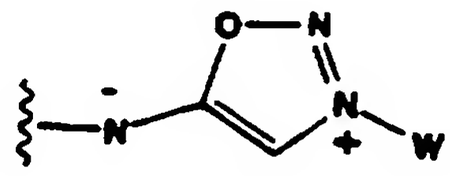


(16) 

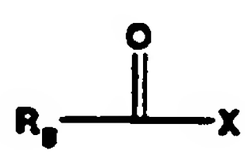
(17) 

in which n is 0 or 1; and

X is (1) -Y-[$C(R_b)(R_c)$]p_1-G-[$C(R_b)(R_c)$]p_2-T-Q, wherein G is (i) a covalent bond; (ii) -T-C(O)-; (iii) -C(O)-T; (iv) -C(Y-C(O)-R_m)- wherein R_m is heteroaryl or heterocyclic ring; p_1 and p_2 are independently selected from p and in which Y, R_b, R_c, p and T are as defined above with the proviso that -T-Q is not -O-NO_2; (2)



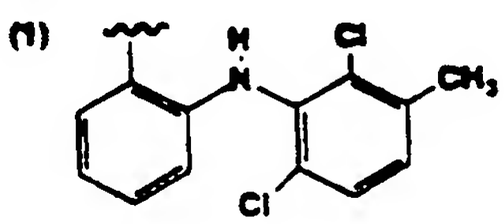
in which W is a heterocyclic ring or NR_hR_i wherein R_h and R_i are independently selected from lower alkyl, aryl or alkenyl; (3) -Y_1[$C(R_b)(R_c)$]$_s$-Z-[C(O)-Y_2-[$C(R_b)(R_c)$]$_{P1}$-T-Q]$_{P2}$ wherein Y_1, and Y_2 are independently selected from Y, S is an integer from 0 to 3, and R_b, R_c, Z, T, and Q are as defined above with the proviso that -T-Q is not is -O-NO_2; and compounds having the structure

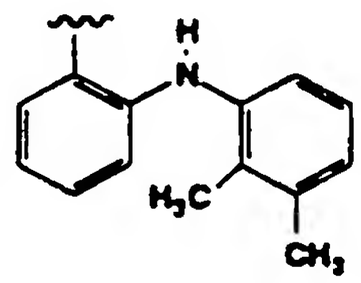


IV

wherein

R_g is selected from

(1) 

(2) 

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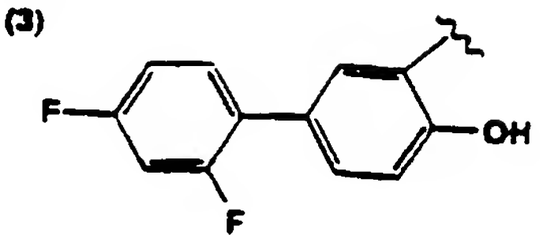
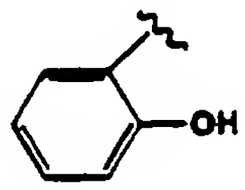


(4)



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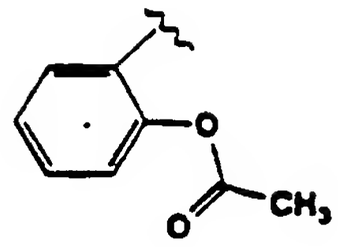

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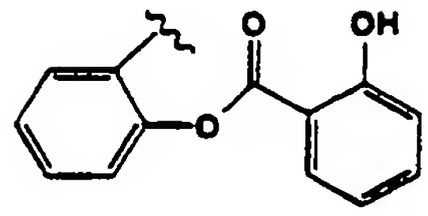

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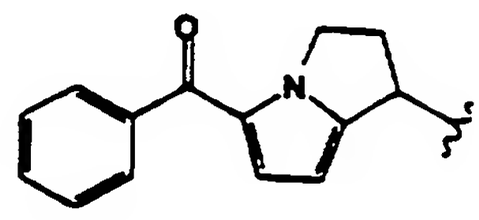


and X is defined as above.

12. The composition of claim 9 wherein the nonsteroidal antiinflammatory drug is selected from the group consisting of salicylic acid derivatives, pyrazolon derivatives, para-aminophenol derivatives, indole derivatives, fentamates, tolmetin, propionic acid derivatives, oxicam derivatives, phenylacetic acid derivatives, cytokine inhibitors, cyclooxygenase inhibitors and selective cyclooxygenase-1 inhibitors as well as cyclooxygenase-2 inhibitors.

13. The composition of claim 12 wherein the salicylic acid derivatives are selected from the group consisting of acetylsalicylic acid, diflunisal, salsalate, sodium salicylate, salicylamide, sodium thiosalicylate, choline salicylate, magnesium salicylate, mesalamine, sulfasalazine and methylsalicylate; the pyrazolon derivatives are selected from the group consisting of phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, dipyrone and apazone; the para-aminophenol derivatives are selected from the group consisting of phenacetin and acetaminophen; the indole derivatives are selected from the group consisting of indomethacin and sulindac; the fentamates are selected from the group consisting of mefenamic, meclofenamic, flufenamic, tolfenamic and etofenamic acids and pharmaceutically acceptable salts thereof; the propionic acid derivatives are selected from the group consisting of ibuprofen, naproxen, flurbiprofen,

fenoprofen. ketoprofen. fenbufen. miroprofen. corprofen. pirprofen. oxaprozin. indoprofen and tiaprofenic acid and pharmaceutically acceptable salts thereof: the oxicam derivatives are selected from the group consisting of piroxicam, isoxicam. amperoxicam, tenoxicam, and the related compound tenidap; the phenylacetic acid derivative is selected from the group consisting of tolmetin and diclofenac and pharmaceutically acceptable salts thereof; the cyclooxygenase inhibitors are selected from the group consisting of etodolac and nabumetone; the selective cyclooxygenase-2 inhibitors are selected from the group consisting of CGP 28238 (6-(2,4-difluorophenoxy)-5- methyl-sulfonylamino -1-indanone), SC-58125 (1-[(4-methylsulfonyl)phenyl]-3- trifluoromethyl-5-(4-fluorophenyl)pyrazole), NS-398 (N-[2-(cyclohexyloxy)- 4-nitro-phenyl]methanesulfonamide), DuP 697 (5-bromo-2-(fluorophenyl)-3-(4- methylsulfonylphenyl) thiophene), L-745,337 (5-methanesulphonamida-6-(2,4-diflurorthiophenyl)-1-indanone), the 1,2-substituted diarylcyclopentene analogues such as 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene; and a quinazolinone.

14. The composition of claim 9 wherein the compound that donates, transfers or releases nitric oxide is a S-nitrosothiol.

15. The composition of claim 14 wherein the S-nitrosothiol is selected from the group consisting of those having the structures:

(i) $CH_3[C(R_b)(R_c)]_xSNO$

wherein x equals 2 to 20 and R_b and R_c are as defined above:

(ii) $HS[C(R_b)(R_c)]_xSNO$

wherein x equals 2 to 20; and

(iii) $ONS[C(R_b)(R_c)]_xV$

wherein x equals 2 to 20 and V is selected from the group consisting of fluoro, alkoxy, cyano, carboxamido, cycloalkyl, arylkoxy, alkylsulfinyl, arylthio, alkylamino,

dialkylamino. hydroxy. carbamoyl. N-alkylcarbamoyl, N.N-dialkylcarbamoyl. amino. hydroxyl, carboxyl, hydrogen. nitro and aryl; and x, R_b and R_c are as defined above.

16. The composition of claim 11 wherein the compound that donates. transfers or releases nitric oxide is selected from the group consisting of:

(i) compounds that include at least one ON-O-, ON-N- or ON-C- group;

(ii) 2-hydroxy-2-nitrosohydrazine which has an $R_{100}R_{200}$-N(O-M^+)-NO group wherein R_{100} and R_{200} include polypeptides, amino acids, sugars, modified and unmodified oligonucleotides, hydrocarbons where the hydrocarbon can be a branched or unbranched, and saturated or unsaturated aliphatic hydrocarbon or an aromatic hydrocarbon, hydrocarbons having one or more substituent groups and heterocyclic compounds; and

(iii) a thionitrate which has the structure R_{100}-(S)-NO_2 wherein R_{100} includes polypeptides. amino acids. sugars, modified and unmodified oligonucleotides. and a hydrocarbon where the hydrocarbon can be a branched or unbranched, and saturated or unsaturated aliphatic hydrocarbon or an aromatic hydrocarbon.

17. A method for treating inflammation, pain, gastrointestinal lesions or fever in an animal in need thereof by administering to the animal a therapeutically effective amount of a nonsteroidal antiinflammatory agent of claim 1.

18. A method for treating inflammation, pain, gastrointestinal lesions or fever in an animal in need thereof by administering to the animal a therapeutically effective amount of a nonsteroidal antiinflammatory agent of claim 2.

19. A method for treating inflammation, pain, gastrointestinal lesions or fever in an animal in need thereof by administering to the animal a therapeutically effective amount of the composition of claim 3.

20. A method for treating inflammation, pain, gastrointestinal lesions or fever in an animal in need thereof by administering to the animal a therapeutically effective amount of the composition of claim 9.

21. A method for treating inflammation, pain, gastrointestinal lesions or fever in an animal in need thereof which comprises co-administering to said animal a therapeutically effective amount of a nonsteroidal antiinflammatory drug and a nonsteroidal antiinflammatory drug gastrointestinal toxicity reducing amount of a compound that donates nitric oxide, transfers nitric oxide, releases nitric oxide, or elevates endogenous synthesis levels of nitric oxide.

22. A method of reducing the gastrointestinal toxicity of nonsteroidal antiinflammatory drugs administered to an animal which comprises co-administering to said animal a nonsteroidal antiinflammatory drug gastrointestinal toxicity reducing amount of a compound that donates nitric oxide, transfers nitric oxide, releases nitric oxide, or elevates endogenous synthesis levels of nitric oxide.

23. A method of reducing the renal toxicity of nonsteroidal antiinflammatory drugs administered to an animal which comprises co-administering to said animal a nonsteroidal antiinflammatory drug renal toxicity reducing amount of a compound that donates nitric oxide, transfers nitric oxide, releases nitric oxide, or elevates endogenous synthesis levels of nitric oxide.

FIG. 1

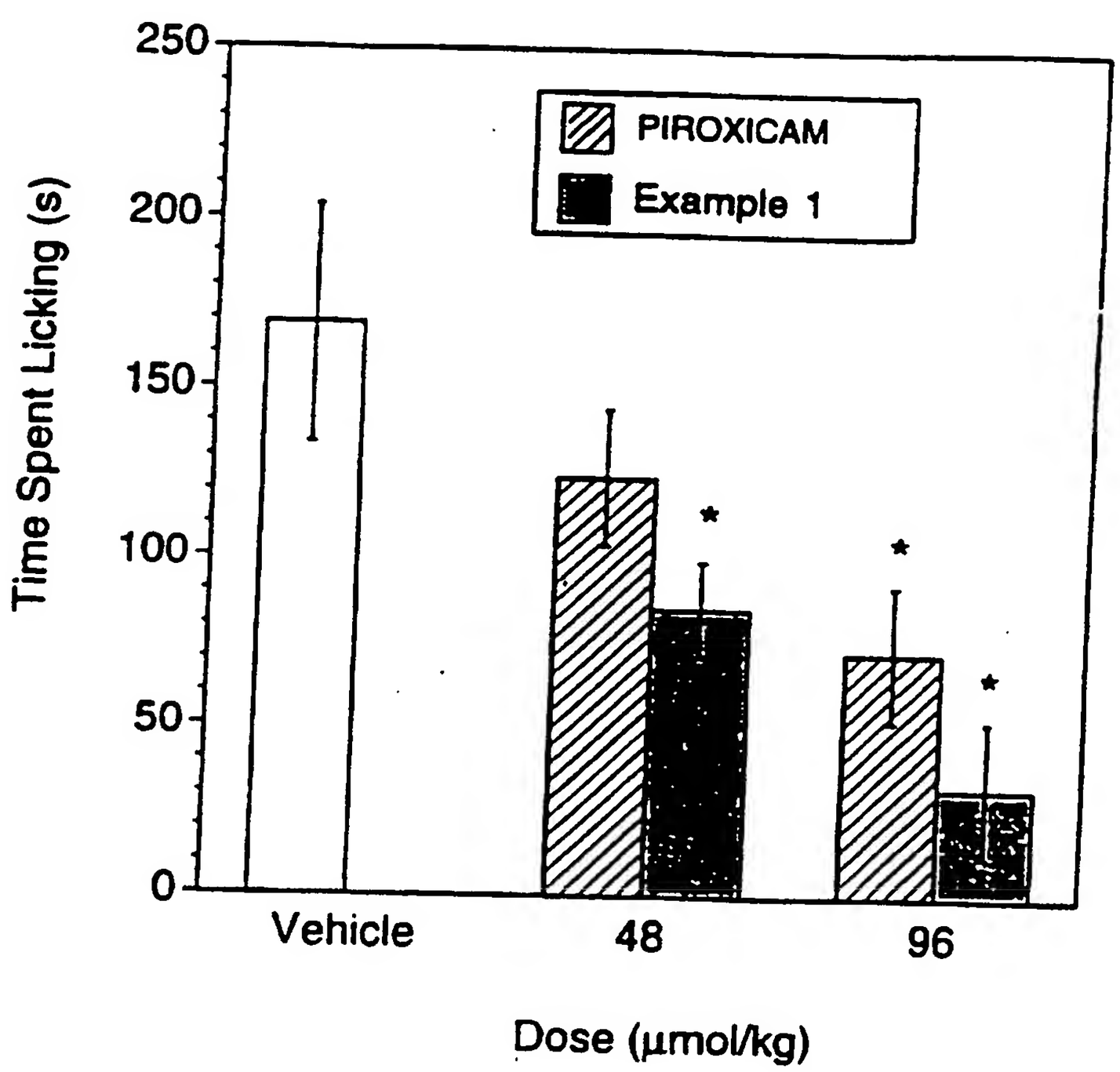
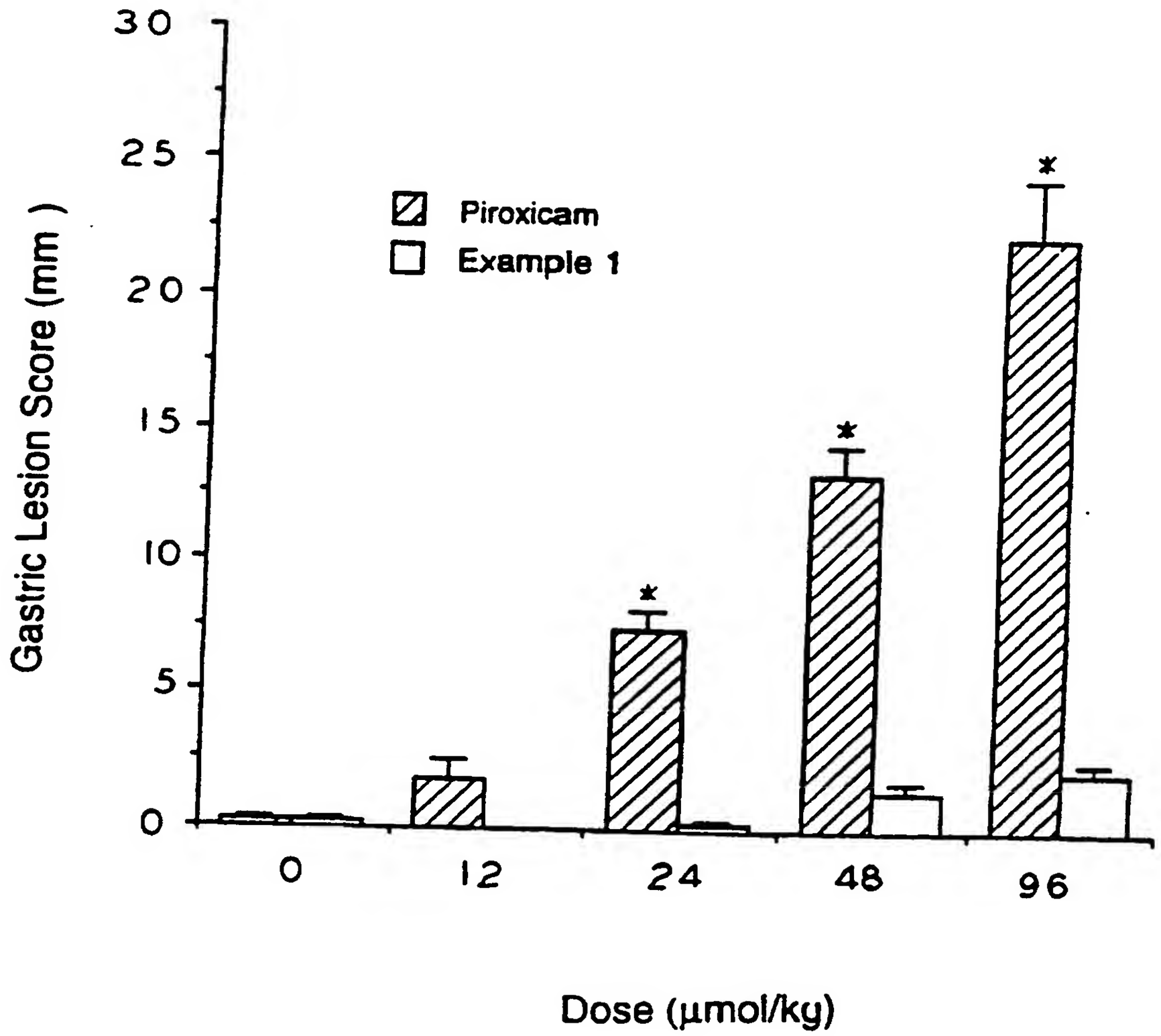

250
200
150
100
50
0
Time Spent Licking (s)
PIROXICAM
Example 1
*
*
*
Vehicle
48
96
Dose (µmol/kg)

FIG. 2


Gastric Lesion Score (mm)
30
25
20
15
10
5
0
Piroxicam
Example 1
*
0
12
24
48
96
Dose (µmol/kg)